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(54) Title: HUMAN SIGNAL PEPTIDE-CONTAINING PROTEINS

(57) Abstract

The invention provides human signal peptide-containing proteins (HSPP) and polynucleotides which indentify and encode HSPP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of HSPP.

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HUMAN SIGNAL PEPTIDE-CONTAINING PROTEINS

TECHNICAL FIELD

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This invention relates to nucleic acid and amino acid sequences of human signal peptidecontaining proteins and to the use of these sequences in the diagnosis, treatment, and prevention of
cell proliferative disorders including cancer; inflammation; and cardiovascular, neurological,
reproductive, and developmental disorders.

BACKGROUND OF THE INVENTION

Protein transport is essential for cellular function. Transport of a protein may be 15 mediated by a signal peptide located at the amino terminus of the protein itself. The signal peptide is comprised of about ten to twenty hydrophobic amino acids which target the nascent protein from the ribosome to a particular membrane bound compartment such as the endoplasmic reticulum (ER). Proteins targeted to the ER may either proceed through the secretory pathway or remain in any of the secretory organelles such as the ER. Golgi apparatus, or lysosomes. Proteins that transit through the secretory pathway are either secreted into the extracellular space or retained in the plasma membrane. Secreted proteins are often synthesized as inactive precursors that are activated by post-translational processing events during transit through the secretory pathway. Such events include glycosylation, phosphorylation, proteolysis, and removal of the signal peptide by a signal 25 peptidase. Other events that may occur during protein transport include chaperonedependent unfolding and folding of the nascent protein and interaction of the protein with a receptor or pore complex. Examples of secreted proteins with amino terminal signal peptides are discussed below and include receptors, extracellular matrix molecules, cytokines, hormones, growth and differentiation factors, neuropeptides, vasomediators, 30 phosphokinases, phosphatases, phospholipases, phosphodiesterases, G and Ras-related proteins, ion channels, transporters/pumps, proteases, and transcription factors. (Reviewed in Alberts. B. et al. (1994) Molecular Biology of The Cell, Garland Publishing, New York, NY, pp. 557-560, 582-592.)

G-protein coupled receptors (GPCRs) comprise a superfamily of integral membrane proteins which transduce extracellular signals. GPCRs include receptors for biogenic amines such as dopamine, epinephrine, histamine, glutamate (metabotropic effect), acetylcholine (muscarinic effect), and serotonin; for lipid mediators of 5 inflammation such as prostaglandins, platelet activating factor, and leukotrienes; for peptide hormones such as calcitonin, C5a anaphylatoxin, follicle stimulating hormone, gonadotropin releasing hormone, neurokinin, oxytocin, and thrombin; and for sensory signal mediators such as retinal photopigments and olfactory stimulatory molecules. The structure of these highly conserved receptors consists of seven hydrophobic 10 transmembrane regions, cysteine disulfide bridges between the second and third extracellular loops, an extracellular N-terminus, and a cytoplasmic C-terminus. The N-terminus interacts with ligands, the disulfide bridges interact with agonists and antagonists, and the large third intracellular loop interacts with G proteins to activate second messengers such as cyclic AMP, phospholipase C, inositol triphosphate, or ion 15 channels. (Reviewed in Watson, S. and Arkinstall, S. (1994) The G-protein Linked Receptor Facts Book, Academic Press, San Diego, CA, pp. 2-6; and Bolander, F.F. (1994) Molecular Endocrinology, Academic Press, San Diego, CA, pp. 162-176.)

Other types of receptors include cell surface antigens identified on leukocytic cells of the immune system. These antigens have been identified using systematic, monoclonal antibody (mAb)-based "shot gun" techniques. These techniques have resulted in the production of hundreds of mAbs directed against unknown cell surface leukocytic antigens. These antigens have been grouped into "clusters of differentiation" based on common immunocytochemical localization patterns in various differentiated and undifferentiated leukocytic cell types. Antigens in a given cluster are presumed to identify a single cell surface protein and are assigned a "CD" number. Some of the genes encoding proteins identified by CD antigens have been isolated and characterized as both transmembrane proteins and cell surface proteins anchored to the plasma membrane via covalent attachment to fatty acid-containing glycolipids such as glycosylphosphatidylinositol (GPI). (Reviewed in Barclay, A. N. et al. (1993) The

Leucocyte Antigen Facts Book, Academic Press, San Diego, CA, pp. 144-145; Noel, L. S. et al. (1998) J. Biol. Chem. 273:3878-3883.)

Tetraspanins are a superfamily of membrane proteins which facilitate the formation

and stability of cell-surface signaling complexes containing lineage-specific proteins, integrins, and other tetraspanins. They are involved in cell activation, proliferation (including cancer), differentiation, adhesion, and motility. These proteins cross the membrane four times, have conserved intracellular – and C-termini and an extracellular,
non-conserved hydrophilic domain. Tetraspanins include, e.g., platelet and endothelial cell membrane proteins, leukocyte surface proteins, tissue specific and tumorous antigens, and the retinitis pigmentosa-associated gene peripherin. (Maecker, H.T. et al. (1997) FASEB J. 11:428-442.)

Matrix proteins (MPs) are transmembrane and extracellular proteins which

function in formation, growth, remodeling, and maintenance of tissues and as important mediators and regulators of the inflammatory response. The expression and balance of MPs may be perturbed by biochemical changes that result from congenital, epigenetic, or infectious diseases. In addition, MPs affect leukocyte migration, proliferation, differentiation, and activation in the immune response. MPs are frequently characterized by the presence of one or more domains which may include collagen-like domains, EGF-like domains, immunoglobulin-like domains, and fibronectin-like domains. In addition, some MPs are heavily glycosylated. MPs include extracellular proteins such as fibronectin. collagen, and galectin and cell adhesion receptors such as cell adhesion molecules (CAMs), cadherins, and integrins. (Reviewed in Ayad, S. et al. (1994) The

Extracellular Matrix Facts Book, Academic Press, San Diego, CA, pp. 2-16; Ruoslahti, E. (1997) Kidney Int. 51:1413-1417; Sjaastad, M.D. and Nelson, W.J. (1997) BioEssays 19:47-55.)

Lectins are proteins characterized by their ability to bind carbohydrates on cell membranes by means of discrete, modular carbohydrate recognition domains, CRDs.

25 (Kishore, U. et al. (1997) Matrix Biol. 15:583-592.) Certain cytokines and membrane-spanning proteins have CRDs which may enhance interactions with extracellular or intracellular ligands, with proteins in secretory pathways, or with molecules in signal transduction pathways. The lipocalin superfamily constitutes a phylogenetically conserved group of more than forty proteins that function by binding to and transporting a variety of physiologically important ligands. (Tanaka, T. et al. (1997) J. Biol. Chem. 272:15789-15795; and van't Hof, W. et al. (1997) J. Biol. Chem. 272:1837-1841.)

Selectins are a family of calcium ion-dependent lectins expressed on inflamed vascular

endothelium and the surface of some leukocytes. (Rossiter, H. et al. (1997) Mol. Med. Today 3:214-222.)

Protein kinases regulate many different cell proliferation, differentiation, and signaling processes by adding phosphate groups to proteins. Reversible protein

5 phosphorylation is a key strategy for controlling protein functional activity in eukaryotic cells. The high energy phosphate which drives this activation is generally transferred from adenosine triphosphate molecules (ATP) to a particular protein by protein kinases and removed from that protein by protein phosphatases. Phosphorylation occurs in response to extracellular signals, cell cycle checkpoints, and environmental or nutritional stresses.

10 Protein kinases may be roughly divided into two groups; protein tyrosine kinases (PTKs) which phosphorylate tyrosine residues, and serine/threonine kinases (STKs) which phosphorylate serine or threonine residues. A few protein kinases have dual specificity. A majority of kinases contain a similar 250-300 amino acid catalytic domain. (Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Book, Vol I, pp. 7-47, Academic Press,

15 San Diego, CA.)

Protein phosphatases remove phosphate groups from molecules previously modified by protein kinases thus participating in cell signaling, proliferation, differentiation, contacts, and oncogenesis. Protein phosphorylation is a key strategy used to control protein functional activity in eukaryotic cells. The high energy phosphate is transferred from ATP to a protein by protein kinases and removed by protein phosphatases. There appear to be three, evolutionarily-distinct protein phosphatase gene families: protein phosphatases (PPs); protein tyrosine phosphatases (PTPs); and acid/alkaline phosphatases (APs). PPs dephosphorylate phosphoserine/threonine residues and are an important regulator of many cAMP mediated, hormone responses in cells.

PTPs reverse the effects of protein tyrosine kinases and therefore play a significant role in cell cycle and cell signaling processes. Although APs dephosphorylate substrates in vitro, their role in vivo is not well known. (Charbonneau, H. and Tonks, N.K. (1992) Annu. Rev. Cell Biol. 8:463-493.)

Cyclic nucleotides (cAMP and cGMP) function as intracellular second messengers
to transduce a variety of extracellular signals, including hormones, light and
neurotransmitters. Cyclic nucleotide phosphodiesterases (PDEs) degrade cyclic
nucleotides to their corresponding monophosphates, thereby regulating the intracellular

concentrations of cyclic nucleotides and their effects on signal transduction. At least seven families of mammalian PDEs have been identified based on substrate specificity and affinity, sensitivity to cofactors and sensitivity to inhibitory drugs. (Beavo, J.A. (1995) Physiological Reviews 75: 725-748.)

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Phospholipases (PLs) are enzymes that catalyze the removal of fatty acid residues from phosphoglycerides. PLs play an important role in transmembrane signal transduction and are named according to the specific ester bond in phosphoglycerides that is hydrolyzed, i.e., A₁, A₂, C or D. PLA₂ cleaves the ester bond at position 2 of the glycerol moiety of membrane phospholipids giving rise to arachidonic acid. Arachidonic acid is 10 the common precursor to four major classes of eicosanoids, namely prostaglandins, prostacyclins, thromboxanes and leukotrienes. Eicosanoids are signaling molecules involved in the contraction of smooth muscle, platelet aggregation, and pain and inflammatory responses. (Alberts, B. et al. (1994) Molecular Biology of The Cell, Garland Publishing, Inc., New York, NY, pp. 85, 211, 239-240, 642-645.)

The nucleotide cyclases, i.e., adenylate and guanylate cyclase, catalyze the synthesis of the cyclic nucleotides, cAMP and cGMP, from ATP and GTP, respectively. They act in concert with phosphodiesterases, which degrade cAMP and cGMP, to regulate the cellular levels of these molecules and their functions. cAMP and cGMP function as intracellular second messengers to transduce a variety of extracellular signals, e.g., hormones, and light and neurotransmitters. (Stryer, L. (1988) Biochemistry W.H. Freeman and Co., New York, pp. 975-980, 1029-1035.)

Cytokines are produced in response to cell perturbation. Some cytokines are produced as precursor forms, and some form multimers in order to become active. They are produced in groups and in patterns characteristic of the particular stimulus or disease, 25 and the members of the group interact with one another and other molecules to produce an overall biological response. Interleukins, neurotrophins, growth factors, interferons, and chemokines are all families of cytokines which work in conjunction with cellular receptors to regulate cell proliferation and differentiation and to affect such activities as leukocyte migration and function, hematopoietic cell proliferation, temperature regulation, acute 30 response to infections, tissue remodeling, apoptosis, and cell survival. Studies using antibodies or other drugs that modify the activity of a particular cytokine are used to elucidate the roles of individual cytokines in pathology and physiology.

Chemokines, in particular, are small chemoattractant cytokines involved in inflammation, leukocyte proliferation and migration, angiogenesis and angiostasis, regulation of hematopoiesis, HIV infectivity, and stimulation of cytokine secretion. Chemokines generally contain 70-100 amino acids and are subdivided into four subfamilies based on the presence of conserved cysteine-based motifs. (Callard, R. and Gearing, A. (1994) The Cytokine Facts Book. Academic Press, New York, NY, pp. 181-190, 210-213, 223-227.)

Growth and differentiation factors are secreted proteins which function in intercellular communication. Some factors require oligomerization or association with 10 MPs for activity. Complex interactions among these factors and their receptors trigger intracellular signal transduction pathways that stimulate or inhibit cell division, cell differentiation, cell signaling, and cell motility. Most growth and differentiation factors act on cells in their local environment (paracrine signaling). There are three broad classes of growth and differentiation factors. The first class includes the large polypeptide growth 15 factors such as epidermal growth factor, fibroblast growth factor, transforming growth factor, insulin-like growth factor, and platelet-derived growth factor. The second class includes the hematopoietic growth factors such as the colony stimulating factors (CSFs). Hematopoietic growth factors stimulate the proliferation and differentiation of blood cells such as B-lymphocytes, T-lymphocytes, erythrocytes, platelets, eosinophils, basophils, 20 neutrophils, macrophages, and their stem cell precursors. The third class includes small peptide factors such as bombesin, vasopressin, oxytocin, endothelin, transferrin, angiotensin II, vasoactive intestinal peptide, and bradykinin which function as hormones to regulate cellular functions other than proliferation.

Growth and differentiation factors play critical roles in neoplastic transformation of
cells in vitro and in tumor progression in vivo. Inappropriate expression of growth factors
by tumor cells may contribute to vascularization and metastasis of melanotic tumors.

During hematopoiesis, growth factor misregulation can result in anemias, leukemias, and
lymphomas. Certain growth factors such as interferon are cytotoxic to tumor cells both in
vivo and in vitro. Moreover, some growth factors and growth factor receptors are related
both structurally and functionally to oncoproteins. In addition, growth factors affect
transcriptional regulation of both proto-oncogenes and oncosuppressor genes. (Reviewed
in Pimentel, E. (1994) Handbook of Growth Factors, CRC Press, Ann Arbor, MI, pp. 1-9.)

Proteolytic enzymes or proteases either activate or deactivate proteins by hydrolyzing peptide bonds. Proteases are found in the cytosol, in membrane-bound compartments, and in the extracellular space. The major families are the zinc, serine, cysteine, thiol, and carboxyl proteases.

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Zinc proteases, e.g., carboxypeptidase A, have a zinc ion bound to the active site. These proteases recognize C-terminal residues that contain an aromatic or bulky aliphatic side chain, and hydrolyze the peptide bond adjacent to the C-terminal residues. Serine proteases have an active site serine residue and include digestive enzymes, e.g., trypsin and chymotrypsin, components of the complement and blood-clotting cascades, and 10 enzymes that control the degradation and turnover of extracellular matrix (ECM) molecules. Cysteine proteases (e.g. cathepsin) are produced by monocytes. macrophages and other immune cells, and are involved in diverse cellular processes ranging from the processing of precursor proteins to intracellular degradation. Overproduction of these enzymes can cause the tissue destruction associated with rheumatoid arthritis and asthma. 15 Thiol proteases, e.g., papain, contain an active site cysteine and are widely distributed within tissues. Carboxyl proteases, e.g., pepsin, are active only under acidic conditions (pH 2 to 3).

Guanosine triphosphate-binding proteins (G proteins) can be grouped into two major classes: heterotrimeric G proteins and small G proteins. Heterotrimeric G proteins 20 interact with GPCRs that respond to hormones, growth factors, neuromodulators, or other signaling molecules. The interaction between GPCR and G protein allows the G protein to exchange GTP for guanosine diphosphate (GDP). This exchange activates the G protein, allowing it to dissociate from the receptor and interact with the its cognate second messenger-generating protein, e.g., adenylate cyclase, guanylate cyclase, phospholipase C, or ion channels. The hydrolysis of GTP to GDP by the G protein acts as an on-off switch, terminating the action of the G protein and preparing it to interact with another receptor molecule, thus beginning another round of signal transduction.

The small G proteins consist of single 21-30 kDa polypeptides. They can be classified into five subfamilies: Ras, Rho, Ran, Rab, and ADP-ribosylation factor. These 30 proteins regulate cell growth, cell cycle control, protein secretion, and intracellular vesicle interaction. In particular, the Ras proteins are essential in transducing signals from receptor tyrosine kinases to serine/threonine kinases which control cell growth and

differentiation. Mutant Ras proteins, which bind but can not hydrolyze GTP, are permanently activated and cause continuous cell proliferation or cancer. All five subfamilies share common structural features and four conserved motifs. Most of the membrane-bound G proteins require a carboxy terminal isoprenyl group (CAAX), added posttranslationally, for membrane association and biological activity. The G proteins also have a variable effector region, located between motifs I and II, which is characterized as the interaction site for guanine nucleotide exchange factors or GTPase-activating proteins.

Eukaryotic cells are bound by a membrane and subdivided into membrane-bound compartments. Membranes are impermeable to many ions and polar molecules, therefore transport of these molecules is mediated by ion channels, ion pumps, transport proteins, or pumps. Symporters and antiporters regulate cytosolic pH by transporting ions and small molecules, e.g., amino acids, glucose, and drugs, across membranes; symporters transport small molecules and ions in the same direction, and antiporters, in the opposite direction. Transporter superfamilies include facilitative transporters and active ATP binding cassette transporters involved in multiple-drug resistance and the targeting of antigenic peptides to MHC Class I molecules. These transporters bind to a specific ion or other molecule and undergo conformational changes in order to transfer the ion or molecule across a membrane. Transport can occur by a passive, concentration-dependent mechanism or can be linked to an energy source such as ATP hydrolysis or an ion gradient.

Ion channels, ion pumps, and transport proteins mediate the transport of molecules across cellular membranes. Symporters and antiporters regulate cytosolic pH by transporting ions and small molecules such as amino acids, glucose, and drugs. Symporters transport small molecules and ions unidirectionally, and antiporters, bidirectionally. Transporter superfamilies include facilitative transporters and active ATP-binding cassette transporters which are involved in multiple-drug resistance and the targeting of antigenic peptides to MHC Class I molecules. These transporters bind to a specific ion or other molecule and undergo a conformational change in order to transfer the ion or molecule across the membrane. Transport can occur by a passive, concentration-dependent mechanism or can be linked to an energy source such as ATP hydrolysis. (Reviewed in Alberts, B. et al. (1994) Molecular Biology of The Cell, Garland Publishing, New York, NY, pp. 523-546.)

Ion channels are formed by transmembrane proteins which create a lined passageway across the membrane through which water and ions, such as Na+, K+, Ca2+, and Cl, enter and exit the cell. For example, chloride channels are involved in the regulation of the membrane electric potential as well as absorption and secretion of ions 5 across the membrane. Chloride channels also regulate the internal pH of membrane-bound organelles.

Ion pumps are ATPases which actively maintain membrane gradients. Ion pumps are classified as P, V, or F according to their structure and function. All have one or more binding sites for ATP in their cytosolic domains. The P-class ion pumps include Ca2+ 10 ATPase and Na⁺/K⁺ ATPase and function in transporting H⁺, Na⁺, K⁺, and Ca²⁺ ions. Pclass pumps consist of two α and two β transmembrane subunits. The V- and F-class ion pumps have similar structures and but transport only H⁺. F class H⁺ pumps mediate transport across the membranes of mitochondria and chloroplasts, while V-class H+ pumps regulate acidity inside lysosomes, endosomes, and plant vacuoles.

A family of structurally related intrinsic membrane proteins known as facilitative glucose transporters catalyze the movement of glucose and other selected sugars across the plasma membrane. The proteins in this family contain a highly conserved, large transmembrane domain comprised of 12 α -helices, and several weakly conserved, cytoplasmic and exoplasmic domains (Pessin, J. E., and Bell, G.I. (1992) Annu. Rev. 20 Physiol. 54:911-930).

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Amino acid transport is mediated by Na⁺ dependent amino acid transporters. These transporters are involved in gastrointestinal and renal uptake of dietary and cellular amino acids and in neuronal reuptake of neurotransmitters. Transport of cationic amino acids is mediated by the system y+ family and the cationic amino acid transporter (CAT) 25 family. Members of the CAT family share a high degree of sequence homology, and each contains 12-14 putative transmembrane domains (Ito, K. and Groudine, M. (1997) J. Biol. Chem. 272:26780-26786).

Proton-coupled, 12 membrane-spanning domain transporters such as PEPT 1 and PEPT 2 are responsible for gastrointestinal absorption and for renal reabsorbtion of 30 peptides using an electrochemical H⁺ gradient as the driving force. A heterodimeric peptide transporter, consisting of TAP 1 and TAP 2, is associated with antigen processing. Peptide antigens are transported across the membrane of the endoplasmic reticulum so

they can be presented to the major histocompatibility complex class I molecules. Each TAP protein consists of multiple hydrophobic membrane spanning segments and a highly conserved ATP-binding cassette. (Boll, M. et al. (1996) Proc. Natl. Acad. Sci. 93:284-289.)

Hormones are secreted molecules that travel through the circulation and bind to 5 specific receptors on the surface of, or within, target cells. Although they have diverse biochemical compositions and mechanisms of action, hormones can be grouped into two categories. One category consists of small lipophilic hormones that diffuse through the plasma membrane of target cells, bind to cytosolic or nuclear receptors, and form a 10 complex that alters gene expression. Examples of these molecules include retinoic acid, thyroxine, and the cholesterol-derived steroid hormones such as progesterone, estrogen, testosterone, cortisol, and aldosterone. The second category consists of hydrophilic hormones that function by binding to cell surface receptors that transduce signals across the plasma membrane. Examples of such hormones include amino acid derivatives such 15 as catecholamines and peptide hormones such as glucagon, insulin, gastrin, secretin, cholecystokinin, adrenocorticotropic hormone, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, and vasopressin. (See, for example, Lodish et al. (1995) Molecular Cell Biology, Scientific American Books Inc., New York, NY, pp. 856-864.)

Neuropeptides and vasomediators (NP/VM) comprise a large family of endogenous signaling molecules. Included in this family are neuropeptides and neuropeptide hormones such as bombesin, neuropeptide Y, neurotensin, neuromedin N, melanocortins, opioids, galanin, somatostatin, tachykinins, urotensin II and related peptides involved in smooth muscle stimulation, vasopressin, vasoactive intestinal peptide, and circulatory system-borne signaling molecules such as angiotensin, complement, calcitonin, endothelins, formyl-methionyl peptides, glucagon, cholecystokinin and gastrin. NP/VMs can transduce signals directly, modulate the activity or release of other neurotransmitters and hormones, and act as catalytic enzymes in cascades. The effects of NP/VMs range from extremely brief to long-lasting. (Reviewed in Martin, C. R. et al.

Regulatory molecules turn individual genes or groups of genes on and off in response to various inductive mechanisms of the cell or organism; act as transcription factors by determining

whether or not transcription is initiated, enhanced, or repressed; and splice transcripts as dictated in a particular cell or tissue. Although they interact with short stretches of DNA scatt red throughout the entire genome, most gene expression is regulated near the site at which transcription starts or within the open reading frame of the gene being expressed. Many of the transcription factors incorporate one of a set of DNA-binding structural motifs, each of which contains either α helices or β sheets and binds to the major groove of DNA. (Pabo, C.O. and R.T. Sauer (1992) Ann. Rev. Biochem. 61:1053-95.) Other domains of transcription factors may form crucial contacts with the DNA. In addition, accessory proteins provide important interactions which may convert a particular protein complex to an activator or a repressor or may prevent binding. (Alberts, B. et al. (1994) Molecular Biology of the Cell, Garland Publishing Co, New York, NY pp. 401-474.)

The discovery of new human signal peptide-containing proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative disorders including cancer; inflammation; and cardiovascular, neurological, reproductive, and developmental disorders.

SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, proteins with signal 20 peptides, referred to collectively as "HSPP" and individually as "HSPP-1", "HSPP-2", "HSPP-3", "HSPP-4", "HSPP-5", "HSPP-6", "HSPP-7", "HSPP-8", "HSPP-9", "HSPP-10", "HSPP-11", "HSPP-12", "HSPP-13", "HSPP-14", "HSPP-15", "HSPP-16", "HSPP-17", "HSPP-18", "HSPP-19", "HSPP-20", "HSPP-21", "HSPP-22", "HSPP-23", "HSPP-24", "HSPP-25", "HSPP-26", "HSPP-27", "HSPP-28", "HSPP-29", "HSPP-30", "HSPP-25 31", "HSPP-32", "HSPP-33", "HSPP-34", "HSPP-35", "HSPP-36", "HSPP-37", "HSPP-38", "HSPP-39", "HSPP-40", "HSPP-41", "HSPP-42", "HSPP-43", "HSPP-44", "HSPP-45", "HSPP-46", "HSPP-47", "HSPP-48", "HSPP-49", "HSPP-50", "HSPP-51", "HSPP-52", "HSPP-53", "HSPP-54", "HSPP-55", "HSPP-56", "HSPP-57", "HSPP-58", "HSPP-59", "HSPP-60", "HSPP-61", "HSPP-62", "HSPP-63", "HSPP-64", "HSPP-65", "HSPP-30 66", "HSPP-67", "HSPP-68", "HSPP-69", "HSPP-71", "HSPP-71", "HSPP-72", "HSPP-73", "HSPP-74", "HSPP-75", HSPP-76", "HSPP-77", "HSPP-78", "HSPP-79", "HSPP-80", "HSPP-81", "HSPP-82", "HSPP-83", "HSPP-84", "HSPP-85", "HSPP-86", "HSPP-87", "HSPP-88", "HSPP-89", "HSPP-90", "HSPP-91", "HSPP-92", "HSPP-93", "HSPP-94", "HSPP-95", "HSPP-96", "HSPP-97", "HSPP-98", "HSPP-99", "HSPP-100", "HSPP-

101", "HSPP-102", "HSPP-103", "HSPP-104", "HSPP-105", "HSPP-106", "HSPP-107", "HSPP-108", "HSPP-109", "HSPP-110", HSPP-111", "HSPP-112", "HSPP-113", "HSPP-114", "HSPP-115", "HSPP-116", "HSPP-117", "HSPP-118", "HSPP-119", "HSPP-120", "HSPP-121", "HSPP-122", "HSPP-123", "HSPP-124", "HSPP-125", "HSPP-126", 5 "HSPP-127", "HSPP-128", "HSPP-129", "HSPP-130", "HSPP-131", "HSPP-132", "HSPP-133", and "HSPP-134". In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID 10 NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO: 28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, 15 SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID 20 NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ 25 ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID 30 NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID

NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134 (SEQ ID NO:1-134), and fragments thereof.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-134, and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-134, and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-134, and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:115 134, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-134, and fragments thereof.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:135, SEQ ID NO:136, SEQ ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEQ ID NO:161, SEQ ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, SEQ ID NO:187, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:195, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:195, SEQ ID NO:191, SEQ ID NO:191, SEQ ID NO:191

NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ ID NO:202, SEQ ID NO:203, SEQ ID NO:204, SEQ ID NO:205, SEQ ID NO:206, SEQ ID NO:207, SEQ ID NO:208, SEQ ID NO:209, SEQ ID NO:210, SEQ ID NO:211, SEQ ID NO:212, SEQ ID NO:213, SEQ ID NO:214, SEQ ID NO:215, SEQ ID 5 NO:216, SEQ ID NO:217, SEQ ID NO:218, SEQ ID NO:219, SEQ ID NO:220, SEQ ID NO:221, SEQ ID NO:222, SEQ ID NO:223, SEQ ID NO:224, SEQ ID NO:225, SEQ ID NO:226, SEQ ID NO:227, SEQ ID NO:228, SEQ ID NO:229, SEQ ID NO:230, SEQ ID NO:231, SEQ ID NO:232, SEQ ID NO:233, SEQ ID NO:234, SEQ ID NO:235, SEQ ID NO:236, SEQ ID NO:237, SEQ ID NO:238, SEQ ID NO:239, SEQ ID NO:240, SEQ ID 10 NO:241, SEQ ID NO:242, SEQ ID NO:243, SEQ ID NO:244, SEQ ID NO:245, SEQ ID NO:246, SEQ ID NO:247, SEQ ID NO:248, SEQ ID NO:249, SEQ ID NO:250, SEQ ID NO:251, SEQ ID NO:252, SEQ ID NO:253, SEQ ID NO:254, SEQ ID NO:255, SEQ ID NO:256, SEQ ID NO:257, SEQ ID NO:258, SEQ ID NO:259, SEQ ID NO:260, SEQ ID NO:261, SEQ ID NO:262, SEQ ID NO:263, SEQ ID NO:264, SEQ ID NO:265, SEQ ID 15 NO:266, SEQ ID NO:267, SEQ ID NO:268 (SEQ ID NO:135-268), and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:135-268, and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is 20 complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:135-268, and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention further provides an expression vector containing at least a fragment
of the polynucleotide encoding the polypeptide comprising an amino acid sequence
selected from the group consisting of SEQ ID NO:1-134, and fragments thereof. In
another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-134, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-134, and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of HSPP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-134, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of HSPP, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-134, and fragments thereof.

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BRIEF DESCRIPTION OF THE TABLE

Table 1 shows nucleotide and polypeptide sequence identification numbers (SEQ ID NO), clone identification numbers (clone ID), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding HSPP.

Table 2 shows features of each polypeptide sequence, including predicted signal peptide sequences, and methods and algorithms used for identification of HSPP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis, diseases, disorders, or conditions associated with these tissues, and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which Incyte cDNA clones encoding HSPP were isolated.

Table 5 shows the programs, their descriptions, references, and threshold parameters used to analyze HSPP.

Table 6 shows the regions of the full-length nucleotide sequences of HSPP to which cDNA fragments of Table 1 correspond.

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DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"HSPP" refers to the amino acid sequences of substantially purified HSPP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which, when bound to HSPP, increases or prolongs the duration of the effect of HSPP. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of HSPP.

An "allelic variant" is an alternative form of the gene encoding HSPP. Allelic

variants may result from at least one mutation in the nucleic acid sequence and may result
in altered mRNAs or in polypeptides whose structure or function may or may not be
altered. Any given natural or recombinant gene may have none, one, or many allelic
forms. Common mutational changes which give rise to allelic variants are generally
ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these
types of changes may occur alone, or in combination with the others, one or more times in
a given sequence.

"Altered" nucleic acid sequences encoding HSPP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as HSPP or a polypeptide with at least one functional characteristic of HSPP.

20 Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding HSPP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding HSPP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent HSPP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of HSPP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine,

isoleucine, and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

The terms "amino acid" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic fragments" refer to fragments of HSPP which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of HSPP. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

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The term "antagonist" refers to a molecule which, when bound to HSPP, decreases the amount or the duration of the effect of the biological or immunological activity of HSPP. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of HSPP.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind HSPP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete

with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence.

Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active," refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic HSPP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

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The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules.

The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" or a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding HSPP or fragments of HSPP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence"refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a 5 computer program for fragment assembly, such as the GELVIEW Fragment Assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence 10 encoding HSPP, by northern analysis is indicative of the presence of nucleic acids encoding HSPP in a sample, and thereby correlates with expression of the transcript from the polynucleotide encoding HSPP.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

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The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is 20 one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an 25 identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the 30 binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require

that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" or "% identity" refer to the percentage of sequence similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR, Madison WI) which creates alignments between two or more sequences 10 according to methods selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988) Gene 73:237-244.) The clustal algorithm groups sequences into clusters by examining the distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by dividing the length of 15 sequence A, minus the number of gap residues in sequence A, minus the number of gap residues in sequence B, into the sum of the residue matches between sequence A and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known 20 in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) Methods Enzymol. 183:626-645.) Identity between sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary

bases. A hybridization complex may be formed in solution (e.g., Cot or Rot analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have 5 been fixed).

The words "insertion" or "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

"Immune response" can refer to conditions associated with inflammation, trauma, 10 immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" or "array element" in a microarray context, refer to 15 hybridizable polynucleotides arranged on the surface of a substrate.

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The term "modulate" refers to a change in the activity of HSPP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of HSPP.

The phrases "nucleic acid" or "nucleic acid sequence," as used herein, refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers 25 to those nucleic acid sequences which, comprise a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:135-268, for example, as distinct from any other sequence in the same genome. For example, a fragment of SEQ ID NO:135-268 is useful in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:135-268 from related polynucleotide sequences. A fragment of 30 SEQ ID NO:135-268 is at least about 15-20 nucleotides in length. The precise length of the fragment of SEQ ID NO:135-268 and the region of SEQ ID NO:135-268 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based

on the intended purpose for the fragment. In some cases, a fragment, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide.

The terms "operably associated" or "operably linked" refer to functionally related

nucleic acid sequences. A promoter is operably associated or operably linked with a

coding sequence if the promoter controls the translation of the encoded polypeptide.

While operably associated or operably linked nucleic acid sequences can be contiguous

and in the same reading frame, certain genetic elements, e.g., repressor genes, are not

contiguously linked to the sequence encoding the polypeptide but still bind to operator

sequences that control expression of the polypeptide.

The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms

15 "amplimer," "primer," "oligomer," and "probe." as these terms are commonly defined in the art.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding HSPP, or fragments thereof, or HSPP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" or "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the

presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be 5 defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term "substantially purified" refers to nucleic acid or amino acid sequences 10 that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

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"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being 25 transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of HSPP polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g.,

replacement of leucine with isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to HSPP. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants.

10 A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state,

THE INVENTION

The invention is based on the discovery of new human signal peptide-containing proteins (HSPP), the polynucleotides encoding HSPP, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative disorders including cancer; inflammation; and cardiovascular, neurological, reproductive, and developmental disorders.

Table I lists the Incyte Clones used to derive full length nucleotide sequences encoding HSPP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NO) of the amino acid and nucleic acid sequences, respectively. Column 3 shows the Clone ID of the Incyte Clone in which nucleic acids encoding each HSPP were identified, and column 4, the cDNA libraries from which these clones were isolated. Column 5

shows Incyte clones, their corresponding cDNA libraries, and shotgun sequences. The clones and shotgun sequences are part of the consensus nucleotide sequence of each HSPP and are useful as fragments in hybridization technologies.

Table 6 shows the regions of the full-length nucleotide sequences of HSPP to

which cDNA fragments of Table 1 correspond. Column 1 lists nucleotide sequence identifiers and column 2 shows the clone ID of the Incyte clone in which nucleic acids encoding each HSPP were identified. Column 3 shows Incyte clones and shotgun sequences which are part of the consensus nucleotide sequence of each HSPP and are useful as fragments in hybridization technologies. Column 4 lists the starting nucleotide position and column 5 the ending nucleotide position of the region of the full-length HSPP to which the cDNA fragment corresponds.

The columns of Table 2 show various properties of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3, potential phosphorylation sites; column 4, potential glycosylation sites; column 5, the amino acid residues comprising signature sequences and motifs; column 6, the identity of each protein; and column 7, analytical methods used to identify each HSPP as a signal peptide-containing protein. Note that in column 5, the first line of each cell lists the amino acid residues comprising predicted signal peptide sequences. Additional identifying motifs or signatures are also listed in column 5. Of particular note is the presence of a glycosyl hydrolase family 9 active site signature in SEQ ID NO:126, a ribosomal protein S18 signature in SEQ ID NO:127, an adrenodoxin family iron-sulfur binding region signature and a cytochrome c family hemebinding site signature in SEQ ID NO:132, and a urotensin II signature sequence in SEQ ID NO:96.

Using BLAST, SEQ ID NO:68 (HSPP-68) has been identified as a TWIK-related acid-sensitive K⁺ channel, and SEQ ID NO:92 (HSPP-92) has been identified as a tyrosine-specific protein phosphatase. The tyrosine-specific protein phosphatases signature in SEQ ID NO:92 (HSPP-92) from about V328 through about F340 (including the putative active site cysteine residue at C330) was identified using BLOCKS and PRINTS. Also of note is the identification of SEQ ID NO:66 (HSPP-66) as a steroid binding protein using BLAST.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding HSPP. The first column of Table 3 lists the nucleotide sequence identifiers. The second column lists tissue categories which express HSPP as a fraction of total tissue categories expressing HSPP. The third column lists the diseases, disorders, or conditions associated with those tissues expressing HSPP. The fourth column lists the vectors used to subclone the cDNA library. Of particular note is the expression of SEQ ID NO:200, SEQ ID NO:203, and SEQ ID NO:225 in lung tissues; the expression of SEQ ID NO:212, SEQ ID NO:216, and SEQ ID NO:220 in reproductive tissues; the expression of SEQ ID NO:223 in cancerous tissues; 10 the expression of SEQ ID NO:232 in gastrointestinal tissue, specifically the small intestine or colon (fifteen out of sixteen (93.8%) cDNA libraries); and the expression of SEQ ID NO:224 in cancerous and proliferating tissues. Also of particular interest is the tissuespecific expression of SEQ ID NO:252 and SEQ ID NO:257. SEQ ID NO:252 is derived from OVARTUT01, an ovarian tumor cDNA library and is exclusively expressed in 15 reproductive tumor tissue. SEQ ID NO:257 is derived from THP1AZT01, a 5-aza-2'-deoxycytidine treated human promonocyte cDNA library and is exclusively expressed in hematopoietic tissue.

The following fragments of the nucleotide sequences encoding HSPP are useful in hybridization or amplification technologies to identify SEQ ID NO:135-268 and to distinguish between SEQ ID NO:135-268 and related polynucleotide sequences. The useful fragments are the fragment of SEQ ID NO:230 from about nucleotide 75 to about nucleotide 104; the fragment of SEQ ID NO:231 from about nucleotide 210 to about nucleotide 239; the fragment of SEQ ID NO:232 from about nucleotide 157 to about nucleotide 186; the fragment of SEQ ID NO:233 from about nucleotide 268 to about nucleotide 297; the fragment of SEQ ID NO:234 from about nucleotide 160 to about nucleotide 186; the fragment of SEQ ID NO:235 from about nucleotide 201 to about nucleotide 230; the fragment of SEQ ID NO:236 from about nucleotide 165 to about nucleotide 194; the fragment of SEQ ID NO:237 from about nucleotide 366 to about nucleotide 395; the fragment of SEQ ID NO:238 from about nucleotide 714 to about nucleotide 743; the fragment of SEQ ID NO:239 from about nucleotide 1731 to about nucleotide 1760; the fragment of SEQ ID NO:240 from about nucleotide 419 to about nucleotide 448; the fragment of SEQ ID NO:241 from about nucleotide 494 to about

nucleotide 523; the fragment of SEQ ID NO:242 from about nucleotide 100 to about nucleotide 129; the fragment of SEQ ID NO:243 from about nucleotide 104 to about nucleotide 133; the fragment of SEQ ID NO:244 from about nucleotide 136 to about nucleotide 165; the fragment of SEQ ID NO:245 from about nucleotide 140 to about 5 nucleotide 169; the fragment of SEQ ID NO:246 from about nucleotide 125 to about nucleotide 154; the fragment of SEQ ID NO:247 from about nucleotide 687 to about nucleotide 758; the fragment of SEQ ID NO:248 from about nucleotide 327 to about nucleotide 398; the fragment of SEQ ID NO:249 from about nucleotide 741 to about nucleotide 785; the fragment of SEQ ID NO:250 from about nucleotide 184 to about 10 nucleotide 255; the fragment of SEQ ID NO:251 from about nucleotide 165 to about nucleotide 242; the fragment of SEQ ID NO:252 from about nucleotide 271 to about nucleotide 342; the fragment of SEQ ID NO:253 from about nucleotide 1081 to about nucleotide 1152; the fragment of SEQ ID NO:254 from about nucleotide 781 to about nucleotide 852; the fragment of SEQ ID NO:255 from about nucleotide 620 to about 15 nucleotide 691; the fragment of SEQ ID NO:256 from about nucleotide 872 to about nucleotide 916; the fragment of SEQ ID NO:257 from about nucleotide 242 to about nucleotide 313; the fragment of SEQ ID NO:258 from about nucleotide 595 to about nucleotide 648; the fragment of SEQ ID NO:259 from about nucleotide 163 to about nucleotide 216; the fragment of SEQ ID NO:260 from about nucleotide 244 to about 20 nucleotide 315; the fragment of SEQ ID NO:261 from about nucleotide 75 to about nucleotide 128; the fragment of SEQ ID NO:262 from about nucleotide 650 to about nucleotide 703; the fragment of SEQ ID NO:263 from about nucleotide 143 to about nucleotide 214; the fragment of SEQ ID NO:264 from about nucleotide 434 to about nucleotide 487; the fragment of SEQ ID NO:265 from about nucleotide 218 to about 25 nucleotide 271; the fragment of SEQ ID NO:266 from about nucleotide 89 to about nucleotide 145; the fragment of SEQ ID NO:267 from about nucleotide 198 to about nucleotide 254; and the fragment of SEQ ID NO:268 from about nucleotide 10 to about nucleotide 54.

The invention also encompasses HSPP variants. A preferred HSPP variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the HSPP amino acid sequence, and which contains at least one functional or structural characteristic of HSPP.

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The invention also encompasses polynucleotides which encode HSPP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:135-268, which encodes HSPP.

The invention also encompasses a variant of a polynucleotide sequence encoding HSPP. In particular, such a variant polynucleotide sequence will have at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding HSPP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:135-268 which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:135-268. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of 15 HSPP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding HSPP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible 20 variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring HSPP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode HSPP and its variants are preferably 25 capable of hybridizing to the nucleotide sequence of the naturally occurring HSPP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding HSPP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or 30 eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding HSPP and its derivatives without altering the encoded amino acid sequences include the

production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode
HSPP and HSPP derivatives, or fragments thereof, entirely by synthetic chemistry. After
production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding HSPP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable 10 of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:135-268 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably 15 less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily 20 include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as 25 needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and $100~\mu\text{g/ml}$ denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 30 % formamide, and 200 μ g/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to 15 practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading 20 exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the Hamilton MICROLAB 2200 (Hamilton, Reno NV), Peltier Thermal Cycler 200 (PTC200; MJ Research, Watertown MA) and the ABI CATALYST 800 (Perkin-Elmer). Sequencing is then carried out using either ABI 373 or 377 DNA 25 sequencing systems (Perkin-Elmer) or the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA). The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding HSPP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect

upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses 5 primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome 10 DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-306). 15 Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate 20 program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g.,

GENOTYPER and SEQUENCE NAVIGATOR. Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode HSPP may be cloned in recombinant DNA molecules that direct expression of HSPP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express HSPP.

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The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter HSPP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding HSPP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232.) Alternatively, HSPP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.)

Automated synthesis may be achieved using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of HSPP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g, Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid

analysis or by sequencing. (See, e.g., Creighton, T. (1984) <u>Proteins, Structures and Molecular Properties</u>, WH Freeman, New York NY.)

In order to express a biologically active HSPP, the nucleotide sequences encoding HSPP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a 5 vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding HSPP. Such elements may vary in their strength and specificity. Specific initiation signals may also be 10 used to achieve more efficient translation of sequences encoding HSPP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding HSPP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding 15 sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) 20 Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding HSPP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding HSPP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral

expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding HSPP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding HSPP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or pSPORT1 plasmid (Life Technologies). Ligation of sequences encoding HSPP into the vector's multiple cloning site disrupts the 10 lacZ gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of HSPP are 15 needed, e.g. for the production of antibodies, vectors which direct high level expression of HSPP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of HSPP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol 20 oxidase, and PGH, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Grant et al. (1987) Methods Enzymol. 153:516-54; and Scorer, C. A. et al. (1994) Bio/Technology 12:181-184.)

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Plant systems may also be used for expression of HSPP. Transcription of sequences encoding HSPP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. 30 et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated

transfection. (See, e.g., <u>The McGraw Hill Yearbook of Science and Technology</u> (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized.

In cases where an adenovirus is used as an expression vector, sequences encoding HSPP

may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses HSPP in host cells.

(See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods

(liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of HSPP in cell lines is preferred. For example, sequences encoding HSPP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines.

These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in tk or apr cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.)

Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, dhfr confers resistance to methotrexate; neo confers resistance to

the aminoglycosides, neomycin and G-418; and als or pat confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., trpB and hisD, 5 which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate B-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding HSPP is inserted within a marker gene sequence, 15 transformed cells containing sequences encoding HSPP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding HSPP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding HSPP and that express HSPP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or 25 quantification of nucleic acid or protein sequences.

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Immunological methods for detecting and measuring the expression of HSPP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, 30 monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on HSPP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al.

(1990) <u>Serological Methods</u>, a <u>Laboratory Manual</u>, APS Press, St Paul MN, Sect. IV; Coligan, J. E. et al. (1997) <u>Current Protocols in Immunology</u>, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) <u>Immunochemical Protocols</u>, Humana Press, Totowa NJ).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding HSPP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding HSPP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding HSPP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode HSPP may be designed to contain signal sequences which direct secretion of HSPP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK,

HEK293, and WI38), are available from the American Type Culture Collection (ATCC, Manassas, VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding HSPP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric HSPP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of HSPP activity. Heterologous protein and peptide moieties may also facilitate 10 purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, cmyc, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, 15 calmodulin, and metal-chelate resins, respectively. FLAG, c-myc, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the HSPP encoding sequence and the heterologous protein sequence, so that 20 HSPP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled HSPP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably 35S-methionine.

Fragments of HSPP may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, <u>supra</u>, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A Peptide

Synthesizer (Perkin-Elmer). Various fragments of HSPP may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

5 Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of HSPP and signal peptide sequences. In addition, chemical and structural similarity, in the context of sequences and motifs, exists between HSPP-66 and prostatic steriod-binding C3 precursor from rat (GI 206453); between HSPP-68 and TWIK-related acid-sensitive K+channel from human (GI 2465542); and between HSPP-92 10 and tyrosine specific protein phosphatases (PROSITE PDOC00323). In addition, the expression of HSPP is closely associated with proliferative, cancerous, inflamed, cardiovascular, nervous, reproductive, hematopoietic/immune, and developmental tissue. Therefore, HSPP appears to play a role in cell proliferative disorders including cancer; inflammation; and cardiovascular, 15 neurological, reproductive, and developmental disorders. In the treatment of cell proliferative disorders including cancer; inflammation; and cardiovascular, neurological, reproductive, and developmental disorders associated with increased HSPP expression or activity, it is desirable to decrease the expression or activity of HSPP. In the treatment of the above conditions associated with decreased HSPP expression or activity, it is desirable to increase the expression or activity of HSPP.

Therefore, in one embodiment, HSPP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HSPP. Examples of such disorders include, but are not limited to, cell proliferative disorders such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia,

gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; inflammatory disorders, such as acquired immunodeficiency syndrome (AIDS), Addison's

disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, 5 dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, 10 polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; cardiovascular disorders including 15 disorders of the blood vessels such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, and vascular tumors; disorders of the heart such as congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve 20 stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, and congenital heart disease; and disorders of the lungs such as congenital lung anomalies, atelectasis, 25 pulmonary congestion and edema, pulmonary embolism, pulmonary hemorrhage, pulmonary infarction, pulmonary hypertension, vascular sclerosis, obstructive pulmonary disease, restrictive pulmonary disease, chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchial asthma, bronchiectasis, bacterial pneumonia, viral and mycoplasmal pneumonia, lung abscess, pulmonary tuberculosis, diffuse 30 interstitial diseases, pneumoconioses, sarcoidosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary

eosinophilia bronchiolitis obliterans-organizing pneumonia, diffuse pulmonary

hemorrhage syndromes, Goodpasture's syndromes, idiopathic pulmonary hemosiderosis, pulmonary involvement in collagen-vascular disorders, pulmonary alveolar proteinosis, lung tumors, inflammatory and noninflammatory pleural effusions, pneumothorax, and pleural tumors; neurological disorders such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, 10 suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other 15 developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathies; myasthenia gravis, periodic paralysis; mental disorders including mood, 20 anxiety, and schizophrenic disorders; akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; reproductive disorders such as disorders of prolactin production; infertility, including tubal disease, ovulatory defects, and endometriosis; disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian 25 hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, carcinoma of the male breast, and gynecomastia; and developmental 30 disorders, such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental

retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spina bifida,

5 anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss.

In another embodiment, a vector capable of expressing HSPP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HSPP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified HSPP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HSPP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of HSPP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of HSPP including, but not limited to, those listed above.

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In a further embodiment, an antagonist of HSPP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of HSPP.

20 Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds HSPP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express HSPP.

In an additional embodiment, a vector expressing the complement of the

25 polynucleotide encoding HSPP may be administered to a subject to treat or prevent a
disorder associated with increased expression or activity of HSPP including, but not
limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act

synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of HSPP may be produced using methods which are generally known in the art. In particular, purified HSPP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind HSPP. Antibodies to HSPP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression 10 library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with HSPP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, 15 various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to HSPP have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small. 25 naturally occurring molecule. Short stretches of HSPP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

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Monoclonal antibodies to HSPP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. 30 These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42;

Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule

5 with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.)

Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce HSPP-specific single chain

10 antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries.

(See, e.g., Burton D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86: 3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for HSPP may also be generated. For example, such fragments include, but are not limited to, F(ab')2 fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the
desired specificity. Numerous protocols for competitive binding or immunoradiometric
assays using either polyclonal or monoclonal antibodies with established specificities are
well known in the art. Such immunoassays typically involve the measurement of complex
formation between HSPP and its specific antibody. A two-site, monoclonal-based
immunoassay utilizing monoclonal antibodies reactive to two non-interfering HSPP
epitopes is preferred, but a competitive binding assay may also be employed (Pound,
supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for HSPP. Affinity is expressed as an association constant, K, which is defined as the molar concentration of HSPP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple HSPP epitopes, represents the average affinity, or avidity, of the antibodies for HSPP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular HSPP epitope, represents a true measure of affinity. Highaffinity antibody preparations with K_a ranging from about 10° to 10¹² L/mole are preferred for use in immunoassays in which the HSPP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10⁶ to 10⁷ L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of HSPP, preferably in active form, from the antibody 15 (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream

20 applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of HSPP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding HSPP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding HSPP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding HSPP. Thus, complementary molecules or fragments may be used to modulate HSPP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and

sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding HSPP.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide

5 sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding HSPP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding HSPP can be turned off by transforming a cell or tissue with

expression vectors which express high levels of a polynucleotide, or fragment thereof,
encoding HSPP. Such constructs may be used to introduce untranslatable sense or
antisense sequences into a cell. Even in the absence of integration into the DNA, such
vectors may continue to transcribe RNA molecules until they are disabled by endogenous
nucleases. Transient expression may last for a month or more with a non-replicating
vector, and may last even longer if appropriate replication elements are part of the vector
system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding HSPP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by

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endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding HSPP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules.

These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding HSPP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life.

Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and
equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or

by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of HSPP, antibodies to HSPP, and mimetics, agonists, antagonists, or inhibitors of HSPP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

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In addition to the active ingredients, these pharmaceutical compositions may

contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be

added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc,

10 polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules

made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as
glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or
binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and,
optionally, stabilizers. In soft capsules, the active compounds may be dissolved or
suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with
or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric,

10 malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of HSPP, such labeling would include amount, frequency, and method of administration.

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Pharmaceutical compositions suitable for use in the invention include compositions
wherein the active ingredients are contained in an effective amount to achieve the intended
purpose. The determination of an effective dose is well within the capability of those
skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example HSPP or fragments thereof, antibodies of HSPP, and agonists, antagonists or inhibitors of HSPP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED₅₀ (the dose therapeutically

effective in 50% of the population) or LD₅₀ (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the LD₅₀/ED₅₀ ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED₅₀ with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 µg to 100,000 µg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

25 DIAGNOSTICS

In another embodiment, antibodies which specifically bind HSPP may be used for the diagnosis of disorders characterized by expression of HSPP, or in assays to monitor patients being treated with HSPP or agonists, antagonists, or inhibitors of HSPP.

Antibodies useful for diagnostic purposes may be prepared in the same manner as

described above for therapeutics. Diagnostic assays for HSPP include methods which utilize the antibody and a label to detect HSPP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled

by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring HSPP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of HSPP expression. Normal or standard values for HSPP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to HSPP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of HSPP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding HSPP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of HSPP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of HSPP, and to monitor regulation of HSPP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting

polynucleotide sequences, including genomic sequences, encoding HSPP or closely
related molecules may be used to identify nucleic acid sequences which encode HSPP.

The specificity of the probe, whether it is made from a highly specific region, e.g., the 5'
regulatory region, or from a less specific region, e.g., a conserved motif, and the
stringency of the hybridization or amplification (maximal, high, intermediate, or low), will

determine whether the probe identifies only naturally occurring sequences encoding
HSPP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the HSPP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:135-268 or from genomic sequences including promoters, enhancers, and introns of the HSPP gene.

Means for producing specific hybridization probes for DNAs encoding HSPP include the cloning of polynucleotide sequences encoding HSPP or HSPP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ³²P or ³⁵S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding HSPP may be used for the diagnosis of 10 disorders associated with expression of HSPP. Examples of such disorders include, but are not limited to, cell proliferative disorders such as actinic keratosis, arteriosclerosis. atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, 15 melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; inflammatory disorders, such as acquired immunodeficiency syndrome (AIDS), Addison's 20 disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyenodocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with 25 lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's 30 syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic,

protozoal, and helminthic infections, and trauma; cardiovascular disorders including disorders of the blood vessels such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, and vascular tumors; disorders of the heart such as congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart 10 disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, and congenital heart disease; and disorders of the lungs such as congenital lung anomalies, atelectasis, pulmonary congestion and edema, pulmonary embolism, pulmonary hemorrhage, pulmonary infarction, pulmonary hypertension, vascular sclerosis, obstructive pulmonary disease, restrictive pulmonary disease, chronic obstructive pulmonary disease, 15 emphysema, chronic bronchitis, bronchial asthma, bronchiectasis, bacterial pneumonia, viral and mycoplasmal pneumonia, lung abscess, pulmonary tuberculosis, diffuse interstitial diseases, pneumoconioses, sarcoidosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary eosinophilia bronchiolitis obliterans-organizing pneumonia, diffuse pulmonary 20 hemorrhage syndromes, Goodpasture's syndromes, idiopathic pulmonary hemosiderosis, pulmonary involvement in collagen-vascular disorders, pulmonary alveolar proteinosis, lung tumors, inflammatory and noninflammatory pleural effusions, pneumothorax, and pleural tumors; neurological disorders such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, 25 dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous 30 system disease; prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome; fatal familial insomnia, nutritional and metabolic diseases

of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal

hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous 5 system disorders, dermatomyositis and polymyositis; inherited, metabolic, endocrine, and toxic myopathies; myasthenia gravis, periodic paralysis; mental disorders including mood, anxiety, and schizophrenic disorders; akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; reproductive disorders such as disorders of prolactin production; infertility, 10 including tubal disease, ovulatory defects, and endometriosis; disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, 15 cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, carcinoma of the male breast, and gynecomastia; and developmental disorders, such as renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental 20 retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Syndenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing 25 loss. The polynucleotide sequences encoding HSPP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered HSPP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding HSPP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding HSPP may be labeled by standard methods and added

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to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding HSPP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with

expression of HSPP, a normal or standard profile for expression is established. This may
be accomplished by combining body fluids or cell extracts taken from normal subjects,
either animal or human, with a sequence, or a fragment thereof, encoding HSPP, under
conditions suitable for hybridization or amplification. Standard hybridization may be
quantified by comparing the values obtained from normal subjects with values from an

experiment in which a known amount of a substantially purified polynucleotide is used.

Standard values obtained in this manner may be compared with values obtained from
samples from patients who are symptomatic for a disorder. Deviation from standard
values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated,

hybridization assays may be repeated on a regular basis to determine if the level of
expression in the patient begins to approximate that which is observed in the normal
subject. The results obtained from successive assays may be used to show the efficacy of
treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding HSPP may involve the use of PCR. These oligomers may be chemically

synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding HSPP, or a fragment of a polynucleotide complementary to the polynucleotide encoding HSPP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may 5 also be employed under less stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

Methods which may also be used to quantitate the expression of HSPP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. 10 Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of 15 the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

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Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. 25 (1997) Proc. Natl. Acad. Sci. 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding HSPP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a 30 specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries.

(See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. 5 (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding HSPP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention 10 may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another 15 mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to 20 a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, HSPP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between HSPP and the agent being 30 tested may be measured.

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Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen,

et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with HSPP, or fragments thereof, and washed. Bound HSPP is then detected by methods well known in the art. Purified HSPP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding HSPP specifically compete with a test compound for binding HSPP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with HSPP.

In additional embodiments, the nucleotide sequences which encode HSPP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all applications, patents, and publications, mentioned above and below, in particular US Ser. No. 60/090,762, US Ser. No. 60/094,983, US Ser. No. 60/102,686, and US Ser. No. 60/112,129, are hereby expressly incorporated by reference.

EXAMPLES

25 I. Construction of cDNA Libraries

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RNA was purchased from Clontech or isolated from tissues described in Table 4.

Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine

isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Valencia CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries 10 were constructed with the UNIZAP vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6). Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate 15 restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 20 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision, using the UNIZAP vector system (Stratagene) or cell lysis. Plasmids were purified using at least one of the following: a MAGIC or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the REAL Prep 96 plasmid kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a Fluoroskan II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

The cDNAs were prepared for sequencing using the ABI CATALYST 800

(Perkin-Elmer) or the HYDRA microdispenser (Robbins Scientific) or MICROLAB 2200

(Hamilton) systems in combination with the PTC-200 thermal cyclers (MJ Research). The cDNAs were sequenced using the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) and standard ABI protocols, base calling software, and kits. In one alternative, cDNAs were sequenced using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics). In another alternative, the cDNAs were amplified and sequenced using the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). In yet another alternative, cDNAs were sequenced using solutions and dyes from Amersham Pharmacia Biotech. Reading frames for the ESTs were determined using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA, extension, and shotgun sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the software programs, descriptions, references, and threshold parameters used. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides a brief description thereof, the third column presents the references which are incorporated by reference herein, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the probability the greater the homology). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR).

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based

on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation, using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probalistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Cur. Opin. Str. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length

15 polynucleotide and amino acid sequences were also used to identify polynucleotide

sequence fragments from SEQ ID NO:135-268. Fragments from about 20 to about 4000

nucleotides which are useful in hybridization and amplification technologies were

described in The Invention section above.

IV. Northern Analysis

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Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, <u>supra</u>, ch. 7; Ausubel, 1995, <u>supra</u>, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ database (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

% sequence identity x % maximum BLAST score

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding HSPP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation/trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific

V. Extension of HSPP Encoding Polynucleotides

Full length nucleic acid sequences of SEQ ID NOs:135-229 were produced by extension of the component fragments described in Table 1, column 5, using oligonucleotide primers based on these fragments. For each nucleic acid sequence, one primer was synthesized to initiate extension of an antisense polynucleotide, and the other was synthesized to initiate extension of a sense polynucleotide. Primers were used to facilitate the extension of the known sequence "outward" generating amplicons containing new unknown nucleotide sequence for the region of interest. The initial primers were designed from the cDNA using OLIGOTM 4.06 (National Biosciences, Plymouth, MN), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries (GIBCO BRL) were used to extend the sequence.

30 If more than one extension is necessary or desired, additional sets of primers are designed to further extend the known region.

High fidelity amplification was obtained by following the instructions for the XL-PCRTM kit (The Perkin-Elmer Corp., Norwalk, CT) and thoroughly mixing the enzyme and reaction mix. PCR was performed using the PTC-200 thermal cycler (MJ Research, Inc., Watertown, MA), beginning with 40 pmol of each primer and the recommended concentrations of all other components of the kit, with the following parameters:

Step 1	94° C for 1 min (initial denaturation)
Step 2	65° C for 1 min
Step 3	68° C for 6 min
Step 4	94° C for 15 sec
Step 5	65° C for 1 min
Step 6	68° C for 7 min
Step 7	Repeat steps 4 through 6 for an additional 15 cycles
Step 8	94° C for 15 sec
Step 9	65° C for 1 min
Step 10	68° C for 7:15 min
Step 11	Repeat steps 8 through 10 for an additional 12 cycles
Step 12	72° C for 8 min
Step 13	4° C (and holding)
	Step 2 Step 3 Step 4 Step 5 Step 6 Step 7 Step 8 Step 9 Step 10 Step 11 Step 12

A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a low concentration (about 0.6% to 0.8%) agarose mini-gel to determine which reactions were successful in extending the sequence. Bands thought to contain the largest products were excised from the gel, purified using QIAQUICKTM (QIAGEN Inc.), and trimmed of overhangs using Klenow enzyme to facilitate religation and cloning.

After ethanol precipitation, the products were redissolved in 13 μl of ligation buffer, 1μl T4-DNA ligase (15 units) and 1μl T4 polynucleotide kinase were added, and the mixture was incubated at room temperature for 2 to 3 hours, or overnight at 16° C. Competent E. coli cells (in 40 μl of appropriate media) were transformed with 3 μl of ligation mixture and cultured in 80 μl of SOC medium. (See, e.g., Sambrook, supra,
Appendix A, p. 2.) After incubation for one hour at 37°C, the E. coli mixture was plated on Luria Bertani (LB) agar (See, e.g., Sambrook, supra, Appendix A, p. 1) containing carbenicillin (2x carb). The following day, several colonies were randomly picked from each plate and cultured in 150 μl of liquid LB/2x carb medium placed in an individual well of an appropriate commercially-available sterile 96-well microtiter plate. The
following day, 5 μl of each overnight culture was transferred into a non-sterile 96-well plate and, after dilution 1:10 with water, 5 μl from each sample was transferred into a PCR

array.

For PCR amplification, 18 μ l of concentrated PCR reaction mix (3.3x) containing 4 units of rTth DNA polymerase, a vector primer, and one or both of the gene specific primers used for the extension reaction were added to each well. Amplification was performed using the following conditions:

5	Step 1	94° C for 60 sec
	Step 2	94° C for 20 sec
	Step 3	55° C for 30 sec
	Step 4	72° C for 90 sec
	Step 5	Repeat steps 2 through 4 for an additional 29 cycles
10	Step 6	72° C for 180 sec
	Step 7	4° C (and holding)

Aliquots of the PCR reactions were run on agarose gels together with molecular weight markers. The sizes of the PCR products were compared to the original partial cDNAs, and appropriate clones were selected, ligated into plasmid, and sequenced.

The full length nucleic acid sequences of SEQ ID NO:230-268 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

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High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg²⁺, (NH₄)₂SO₄, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as

follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:135-268 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

5 VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:135-268 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-32P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10⁷ counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba1, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. After XOMAT-AR film (Eastman Kodak, Rochester NY) is exposed to the blots to film for several hours, hybridization patterns are compared visually.

25 VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of

complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be 5 selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

Complementary Polynucleotides VIII.

Sequences complementary to the HSPP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring HSPP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the 20 coding sequence of HSPP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the HSPP-encoding transcript.

25 IX. **Expression of HSPP**

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Expression and purification of HSPP is achieved using bacterial or virus-based expression systems. For expression of HSPP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are 30 not limited to, the trp-lac (tac) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the lac operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria

express HSPP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG).

Expression of HSPP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding HSPP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems. HSPP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from HSPP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified HSPP obtained by these methods can be used directly in the following activity assay.

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X. Demonstration of HSPP Activity HSPP-68

HSPP-68 activity is measured by determining the potassium current using voltage clamp analysis on single Xenopus laevis oocytes injected with HSPP-68 cRNA. HSPP-68 cRNA is synthesized in vitro from linearized HSPP-68 encoding plasmids using the T7

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RNA polymerase and injected into oocytes.. Injected oocytes are used two to four days after injection. In a 0.3 ml perfusion chamber, a single oocyte is impaled with two standard microelectrodes (1-2.5 MΩ) filled with 3 M KCl. The oocyte is maintained under voltage clamp by using a Dagan TEV 200 amplifier, in buffer containing 96 mM NaCl, 2 mM KCl, 1.8 mM CaCl₂, 2 mM MgCl₂, 5 mM HEPES, pH 7.4 with NaOH. Stimulation of the preparation, data acquisition, and analysis is performed using a computer. All experiments are performed at room temperature (21-22 °C). Following a depolarizing pulse, the characteristics of the resulting potassium current are measured via the recording electrode. The amount of potassium current that flows in response to a unit depolarization is proportional to the activity of HSPP-68 in the cell. (Duprat, F. et al. (1997) EMBO J. 16:5464-5471.)

HSPP-92

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HSPP-92 protein phosphatase activity is measured by the hydrolysis of Pnitrophenyl phosphate (PNPP). HSPP-92 is incubated together with PNPP in HEPES buffer pH 7.5, in the presence of 0.1% b-mercaptoethanol at 37°C for 60 min. The reaction is stopped by the addition of 6 ml of 10 N NaOH and the increase in light absorbance at 410 nm resulting from the hydrolysis of PNPP is measured using a spectrophotometer. The increase in light absorbance is proportional to the activity of PP in the assay. (Diamond R.H. et al (1994) Mol Cell Biol 14:3752-62.)

Alternatively, HSPP, or biologically active fragments thereof, are labeled with 125I Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HSPP, washed, and any wells with labeled HSPP complex are assayed. Data obtained using different concentrations of HSPP are used to calculate values for the 25 number, affinity, and association of HSPP with the candidate molecules.

Alternatively, an assay for HSPP activity measures the expression of HSPP on the cell surface. cDNA encoding HSPP is subcloned into an appropriate mammalian expression vector suitable for high levels of cDNA expression. The resulting construct is transfected into a nonhuman cell line such as NIH3T3. Cell surface proteins are labeled 30 with biotin using methods known in the art. Immunoprecipitations are performed using HSPP-specific antibodies, and immunoprecipitated samples are analyzed using SDS-PAGE and immunoblotting techniques. The ratio of labeled immunoprecipitant to

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unlabeled immunoprecipitant is proportional to the amount of HSPP expressed on the cell surface.

Alternatively, an assay for HSPP activity measures the amount of HSPP in secretory, membrane-bound organelles. Transfected cells as described above are harvested and lysed. The lysate is fractionated using methods known to those of skill in the art, for example, sucrose gradient ultracentrifugation. Such methods allow the isolation of subcellular components such as the Golgi apparatus, ER, small membrane-bound vesicles, and other secretory organelles. Immunoprecipitations from fractionated and total cell lysates are performed using HSPP-specific antibodies, and immunoprecipitated samples are analyzed using SDS-PAGE and immunoblotting techniques. The concentration of HSPP in secretory organelles relative to HSPP in total cell lysate is proportional to the amount of HSPP in transit through the secretory pathway.

XI. Functional Assays

HSPP function is assessed by expressing the sequences encoding HSPP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, preferably 20 of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP, and to evaluate properties, for example, their apoptotic state. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as 30 measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in

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expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York 5 NY.

The influence of HSPP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding HSPP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently 10 separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding HSPP and other genes of interest can be analyzed by northern analysis or microarray techniques.

15 XII. Production of HSPP Specific Antibodies

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HSPP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the HSPP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 25 1995, <u>supra</u>, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A Peptide Synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, supra.) Rabbits are 30 immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide activity by, for example, binding the peptide to plastic,

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blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification f Naturally Occurring HSPP Using Specific Antibodies

Naturally occurring or recombinant HSPP is substantially purified by

5 immunoaffinity chromatography using antibodies specific for HSPP. An immunoaffinity column is constructed by covalently coupling anti-HSPP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing HSPP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of HSPP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/HSPP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and HSPP is collected.

15 XIV. Identification of Molecules Which Interact with HSPP

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HSPP, or biologically active fragments thereof, are labeled with ¹²⁵I

Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) Biochem. J. 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled HSPP, washed, and any wells with labeled HSPP complex are assayed. Data obtained using different concentrations of HSPP are used to calculate values for the number, affinity, and association of HSPP with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

TABLE

		Te	\ _	T					T	T	T	T	
Fragments	443531H1 (MPHGNOT03), 1406807F6 (LATRTUT02), 443531T6 (MPHGNOT03), SBBA00451F1, SBBA00676F1	632860H1 (NEUTGMT01), 784715R3 (PROSNOT05), 509590H1 (MPHGNOT03)	670010H1 (CRBLNOT01), 669971R1 (CRBLNOT01), 1553045F1 (BLADTUT04)	726498H1 (SYNOOAT01), 726498R6 (SYNOOAT01), 866599R3 (BRAITUT03)	795064H1 (OVARNOT03), 4339458H1 (BRAUNOT02), 937605R3 (CERVNOT01), 2381151F6 (ISLTNOT01), 1466346F6 (PANCT11702)	924925H1 (BRAINOT04), 3268330H1 (BRAINOT20) 759120R3 (BRAINOT22)	962390H1 (BRSTTUT03), 1907958F6 (CONNTUT01), 023569F1 (ADENINB01), 167282F1 (LIVRNOT01), 1309211F1 (COLNFET02), SAUA00696F1, SAUA02860F1	1259405H1 (MENITUT03), 2472425H1 (THPINOT03), 774303R1 (COLNNOT05), 1520779F1 (BLADTUT04), 1693833F6 (COLNNOT23), 1831858T6.comp (THPIAZT01), 1527737T6 comp (11CMC1 sT01)	1297384HI (BRSTNOT07), 1269310F6 (BRAINOT09), 1457367FI (COLNFET02), 415587RI (BRSTNOT01). SANA02967FI	1299627H1 (BRSTNOT07), 1359140F6 (LUNGNOT09), 1349224F1 (LATRTUT02), SBAA01431F1, SBAA02909F1, SBAA01156F1	1306026H1 (PLACNOT02), 1464088R6 (PANCNOT04), SBAA02496F1, SBAA04305F1	1316219H1 (BLADTUT02), 2458603F6 (ENDANOT01), 2504756T6 (CONUTUT01)	1329031H1 (PANCNOT07), 1329031T6 (PANCNOT07), 1329031F6
Library	MPHGNOT03	NEUTGMT01	CRBLNOT01	SYNOOAT01	OVARNOT03	BRAINOT04	BRSTTUT03	MENITUT03	BRSTNOT07	BRSTNOT07	PLACNOT02	BLADTUT02	PANCNOT07
Clone ID	443531	632860	670010	726498	795064	924925	962390	1259405	1297384	1299627	1306026	1316219	1329031
Nucleotide SEQ ID NO:	135	136	137	138	139	140	141	142	143	144	145	146	147
Protein SEQ ID NO:	_	2	3	4	S.	9	7	œ	6	01	=	12	13

Fragments	1483050H1 (CORPNOT02), 855049H1 (NGANNOT01), 077017F1 (SYNORAB01), 1483050F6 (CORPNOT02), 1480024T6 (CORPNOT02), 1483050T6 (CORPNOT02), 759486R1 (BRAITUT02)	1514160H1 (PANCTUT01), 1866765T7 (SKINBIT01), 782676R1 (MYOMNOT01), 008055X4 (HMCINOT01), 008055X5 (HMCINOT01), 1866765F6 (SKINBIT01), SAOA03127F1	1603403H1 (LUNGNOT15), 372910F1 (LUNGNOT02), 733299R7 (LUNGNOT03)	1652303HI (PROSTUT08), 1671806HI (BLADNOT05), 1341743TI (COLNTUT03), 3803812HI (BLADTUT03), 1878546F6 (LEUKNOT03), 1428640FI (SINTBST01), 2058609R6 (OVARNOT03), 1331621FI (PANCNOT07), 1306331TI (PLACNOT02)	1693358H1 (COLNNOT23), 2498265H1 (ADRETUT05), 1867125F6 (SKINBIT01), 1693358T6 (COLNNOT23), 2245848R6 (HIPONON02)	1707711H1 (DUODNOT02), 1484609T1 (CORPNOT02), 1707711F6 (DUODNOT02), 1267959F1 (BRAINOT09), 1484609F1 (CORPNOT02), SAJA00930F1, SAJA01300R1, SAJA00999R1	1738735H1 (COLNNOT22), SAJA00944R1, SAJA00137F1, SAJA03629F1	1749147H1 (STOMTUT02), 1749147F6 (STOMTUT02), 1749147T6 (STOMTUT02)	1817722H1 (PROSNOT20), 2011085H1 (TESTNOT03)	1831290HI (THPIAZTOI), 3473958HI (LUNGNOT27), 1972268F6 (UCMCLSTOI), 1301277FI (BRSTNOT07), 1521574FI (BLADTUT04), 1561690T6 (SPLNNOT04), 89146IRI (STOMTUT0I)
Library	CORPNOT02	PANCTUT01	LUNGNOTIS	PROSTUT08	COLNNOT23	DUODNOT02	COLNNOT22	STOMTUT02	PROSNOT20	THP1AZT01
Clone ID	1483050	1514160	1603403	1652303	1693358	170711	1738735	1749147	1817722	1831290
Nucleotide SEQ ID NO:	148	149	150	151	152	153	154	155	156	157
Protein SEQ ID NO:	41	15	16	-/6-	18	61	20	21	22	23

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Fragments	1831477H1 (THP1AZT01), 1582867H1 (DUODNOT01), 1336769T1 (COLNNOT13), 1933092H1 (COLNNOT16), 1519909F1 (BLADTUT04), 1220946H1 (NEUTGMT01), 809556T1 (LUNGNOT04), 1217559T1 (NEUTGMT01), 1309225F1 (COLNFET02)	1841607H1 (COLNNOT07), SBHA03588F1	1852391H1 (LUNGFET03), 734140H1 (TONSNOT01), 1852391F6 (LUNGFET03)	1854555H1 (HNT3AZT01), 2511711H1 (CONUTUT01), 782453R1 (MYOMNOT01), 1854555F6 (HNT3AZT01), 1840675T6 (COLNNOT07), 2109736H1 (BRAITUT03)	1855755H1 (PROSNOT18), 3040236H1 (BRSTNOT16), 1283207F1 (COLNNOT16), 833763T1 (PROSNOT07), 1920926R6 (BRSTTUT01)	1861434H1 (PROSNOT19), 980291R1 (TONGTUT01), 1861434T6 (PROSNOT19), SARA01525F1, SARA02548F1	1872334H1 (LEUKNOT02), 1872334F6 (LEUKNOT02), SBGA03684F1	1877230HI (LEUKNOT03), 2519841HI (BRAITUT21), 1877230T6 (LEUKNOT03), 1254693FI (LUNGFET03), 077020RI (SYNORAB01), 1232336FI (LUNGFET03), 1004952R6 (BRSTNOT03), SARA01879FI, SARA02654FI	1877885H1 (LEUKNOT03), 508020F1 (TMLR3DT01), 2751126R6 (THP1AZS08), SARA02571F1	1889269H1 (BLADTUT07), 1915551H1 (PROSTUT04), 629493X12 (KIDNNOT05), 1441289F1 (THYRNOT03), 1215274X34F1 (BRSTTUT01), 1818447F6 (PROSNOT20), 1208463R1 (BRSTNOT02)	1890243H1 (BLADTUT07), SARA01884F1, SATA00046F1, SARA03294F1, SARA02790F1
Library	THP1AZT01	COLNNOT07	LUNGFET03	HNT3AZT01	PROSNOT18	PROSNOT19	LEUKNOT02	LEUKNOT03	LEUKNOT03	BLADTUT07	BLADTUT07
Clone ID	1831477	1841607	1852391	1854555	1855755	1861434	1872334	1877230	1877885	1889269	1890243
Nucleotide SEQ ID NO:	158	159	160	161	162	163	164	165	991	167	891
Protein SEQ ID NO:	24	25	26	. 27	80 -77-	29	30	31	32	33	34

45 179 2457682 ENDANOT01 2457682H1 (ENDANOT01), 2457682F6 (ENDANOT01)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
47	181	2503743	CONUTUTOI	2503743H1 (CONUTUT01), 1853909H1 (HNT3AZT01), 1517619F1 (PANCTUT01), 1467896F6 (PANCTUT02), 490031F1 (HNT2AGT01), 1208654R1 (BRSTNOT02), 880544R1 (THYRNOT02)
48	182	2537684	BONRTUT01	2537684HI (BONRTUT01), 2005493HI (TESTNOT03), 730969HI (LUNGNOT03), 253760IF6 (BONRTUT01), 916487HI (BRSTNOT04), 996135RI (KIDNTUT01), 1920738R6 (BRSTTUT01), 1957710F6 (CONNNOT01)
. 49	183	2593853	OVARTUT02	2593853H1 (OVARTUT02), 807497H1 (STOMNOT02), 914020R6 (STOMNOT02), 889992R1 (STOMTUT01)
90	184	2622354	KERANOT02	2622354H1 (KERANOT02), 2623992H1 (KERANOT02), 1556510F6 (BLADTUT04)
15	185	2641377	LUNGTUT08	2641377H1 (LUNGTUT08), 4341415H2 (BRAUNOT02), SBCA07049F3
52	186	2674857	KIDNNOT19	2674857HI (KIDNNOTI9), 1872373HI (LEUKNOT02), 470512R6 (MMLRIDT01), 1728547HI (PROSNOT14), 3013651F6 (MUSCNOT07), SBCA01366FI, SBCA00694FI
53	187	2758485	THPIAZS08	2758485H1 (THP1AZS08), 3097533H1 (CERVNOT03), 1578959F6 (DUODNOT01)
54	188	2763296	BRSTNOT12	2763296H1 (BRSTNOT12), 3486025F6 (KIDNNOT31), SBDA07002F3
55	189	2779436	OVARTUT03	2779436H1 (OVARTUT03), 2779436F6 (OVARTUT03), SBDA07009F3
56	190	2808528	BLADTUT08	2808528H1 (BLADTUT08), 2611513F6 (THYMNOT04), SBDA07021T3
57	191	2809230	BLADTUT08	2809230H1 (BLADTUT08), 2213849H1 (SINTFET03), 711706R6 (SYNORAT04), 958323R1 (KIDNNOT05), 030732F1 (THPINOB01)
58	192	2816821	BRSTNOT14	2816821H1 (BRSTNOT14), 3746964H1 (THYMNOT08), 2816821F6 (BRSTNOT14), 948722T6 (PANCNOT05), 807947R6 (STOMNOT02)

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otide Clone ID Library Fragments	6 1910668 CONNTUT01 1269346H1 (BRAINOT09), 1380872F1 (BRAITUT08), 1910668F6 (CONNTUT01), 1910668H1 (CONNTUT01), SATA02800F1, SATA03799F1, SARA02035F1	7 1955143 CONNNOT01 1955143F6 (CONNNOT01), 1955143H1 (CONNNOT01)	8 1961637 BRSTNOT04 867025HI (BRAITUT03), 1961637HI (BRSTNOT04), 2809064T6 (BLADTUT08), 2938714HI (THYMFET02), 2956402HI (KIDNFET01), 3808735T6 (CONTTUT01)	9 1990762 CORPNOT02 1990762H1 (CORPNOT02), 1990762T3 (CORPNOT02), SBGA04911F1, SBGA01201F1, SBGA02205F1	0 1994131 CORPNOT02 1994131H1 (CORPNOT02), 2645984F6 (OVARTUT04)	1997745 BRSTTUT03 1752307F6 (LIVRTUT01), 1853730H1 (HNT3AZT01), 1997745H1 (BRSTTUT03), SAZA00953F1	2 2009035 TESTNOT03 2009035H1 (TESTNOT03), 2009035R6 (TESTNOT03)	3 2009152 TESTNOT03 2009152H1 (TESTNOT03), 2009152R6 (TESTNOT03), 2783263H1 (BRSTNOT13)	4 2061752 OVARNOT03 2061752H1 (OVARNOT03), 2061752T6 (OVARNOT03), 2732805H1 (OVARTUT04), SAZA01310F1, SAZA00830F1	2061933 OVARNOT03 046580R1 (CORNNOT01), 746061R1 (BRAITUT01), 826996R1 (PROSNOT06), 2061933H1 (OVARNOT03)	2081422 UTRSNOT08 2081422F6 (UTRSNOT08), 2081422H1 (UTRSNOT08), SBCA04793F1, SBCA05657F1, SBDA00065F1	2101278 BRAITUT02 2101278HI (BRAITUT02), SAXA00399FI, SAXA01284FI, SAXA01227FI	2121353 BRSTNOT07 341437H1 (NEUTFMT01), 687136H1 (UTRSNOT02), 2121353H1 (BRSTNOT07), SASA01311F1
Nucleotide SEQ ID NO:	206 191	207 195	208 196	209 1990	210 199	211 199.	212 2009	213 2006	214 2061	215 2061	216 2081	217 2101	218 2121
Protein N SEQ ID NO: SI	72	73	74	75	76	7.1	78	79	80	81	82	83	84

Fragments	833263HI (PROSTUT04), 2241736HI (PANCTUT02), SAZA01148FI, SASA03299FI, SASA01349FI	2271935H1 (PROSNON01), 2276774H1 (PROSNON01), 2760171T6 (THP1AZS08)	2295344H1 (BRSTNOT05), 3288561F6 (BONRFET01), SBGA01801F1	905482T1 (COLNNOT08), 1858636F6 (PROSNOT18), 2303994H1 (BRSTNOT05)	2497805F6 (ADRETUT05), 2497805H1 (ADRETUT05)	1754702H1 (LIVRTUT01), 2640776T6 (LUNGTUT08), 2646362H1 (LUNGTUT11), 3356773H1 (PROSTUT16)	2657146F6 (LUNGTUT09), 2657146H1 (LUNGTUT09)	288436R1 (EOSIHET02), 1252824F6 (LUNGFET03), 1305549H1 (PLACNOT02), 1364975R1 (SCORNON02), 2018293H1 (THP1NOT01), 2047320H1 (THP1T701), 2184537F6 (SININOT01), 2755786H1 (THP1AZS08), 4111022H1 (PROSBPT07)	2831245H1 (TLYMNOT03), SBMA01396F1	126263F1 (LUNGNOT01), 2729942H1 (OVARTUT04), 3116250H1 (LUNGTUT13)	3129630F6 (LUNGTUT12), 3129630H1 (LUNGTUT12), SBDA06436F1	007632HI (HMCINOT01), 007632R6 (HMCINOT01), 007632T6 (HMCINOT01)	1236968H1 (LUNGFET03), SBAA02713F1, SBAA03203F1, SBAA04196F1	776410R1 (COLNNOT05), 1334153H1 (COLNNOT13), 1334153T1 (COLNNOT13), 1800085F6 (COLNNOT27), 2701948H1 (OVARTUT10)
Library	PANCTUT02	PROSNON01	BRSTNOT05	BRSTNOT05	ADRETUT05	LUNGTUTII	LUNGTUT09	THP1AZS08	TLYMNOT03	LUNGTUT13	LUNGTUT12	HMC1NOT01	LUNGFET03	COLNNOT13
Clone ID	2241736	2271935	2295344	2303994	2497805	2646362	2657146	2755786	2831245	3116250	3129630	007632	1236968	1334153
Nucleotide SEQ ID NO:	219	220	221	222	223	224	225	226	227	228	229	230	231	232
Protein SEQ ID NO:	85	98	87	88	89	06	16	92	93	94	95	96	76	86

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
66	233	1396975	BRAITUT08	864113H1 (BRAITUT03), 876139R1 (LUNGAST01), 1268313F1 (BRAINOT09), 1351348T1 (LATRTUT02), 1396975H1 (BRAITUT08), 1485768F6 (CORPNOT02), 1815364F6 (PROSNOT20)
100	234	1501749	SINTBST01	079080R1 (SYNORAB01), 1501749H1 (SINTBST01), 1724970H1 (PROSNOT14)
101	235	1575240	LNODNOT03	081858R1 (SYNORAB01), 1575240H1 (LNODNOT03), 3451462R6 (UTRSNON03)
. 102	236	1647884	PROSTUT09	1647884H1 (PROSTUT09), 1647884T6 (PROSTUT09), 3998922R6 (HNT2AZS07)
103	237	1661144	BRSTNOT09	720941X17 (SYNOOAT01), 1661144H1 (BRSTNOT09), 2181782H1 (SININOT01)
104	238	1685409	PROSNOT15	755203RI (BRAITUT02), 1226185TI (COLNNOT01), 1300837FI (BRSTNOT07), 1685409HI (PROSNOT15), 1705256HI (DUODNOT02)
105	239	1731419	BRSTTUT08	1731419H1 (BRSTTUT08), 1731419X319T3 (BRSTTUT08), 1731419X322F1 (BRSTTUT08), 1731419X326F1 (BRSTTUT08), 1731419X329F1 (BRSTTUT08), 1733786F6 (BRSTTUT08), SZAH01494F1
901	240	2650265	BRSTNOT14	1680316T6 (STOMFET01), 2650265H1 (BRSTNOT14), 2650265T6 (BRSTNOT14), 2760588R6 (BRAINOS12)
107	241	2677129	KIDNNO119	1592129H1 (CARGNOT01), 2645962H1 (OVARTUT04), 2677129F6 (KIDNNOT19), 2677129H1 (KIDNNOT19), 2910973H1 (KIDNTUT15), 4571722H1 (PROSTMT02), 4906791H2 (TLYMNOT08)
108	242	3151073	ADRENON04	3150857T6 (ADRENON04), 3151073H1 (ADRENON04), 3151073R6 (ADRENON04)
109	243	3170095	BRSTNOT18	3170095F6 (BRSTNOT18), 3170095H1 (BRSTNOT18)

Fragments	079680F1 (SYNORAB01), 443811T6 (MPHGNOT03), 1509356T6 (LUNGNOT14), 1873596F6 (LEUKNOT02), 2440867H1 (EOSITXT01), 3475168H1 (LUNGNOT27)	446637H1 (MPHGNOT03), 1219376R6 (NEUTGMT01), 3735467F6 (SMCCNOS01), 3735467T6 (SMCCNOS01), 3836893H1 (DENDTNT01)	2129415T6 (KIDNNOT05), 4072159F6 (KIDNNOT26), 4072159H1 (KIDNNOT26)	620937R6 (PGANNOT01), 1003916H1 and 1003916R6 (BRSTNOT03), 1413623H1 (BRAINOT12), 1435945F1 (PANCNOT08), 1479127F1 (CORPNOT02), 1969146R6 (BRSTNOT04), 2517587F6 (BRAITUT21), 2967848H1 (SCORNOT04)	489651H1 (HNTZAGT01), 1265353T1 (SYNORAT05), 1431505R6 (BEPINON01), 1605237F6 (LUNGNOT15), 2093492H1 and 2093492T6 (PANCNOT04), 4195560H1 (COLITUT02)	2108789H1 and 2108789R6 (BRAITUT03), 2182008T6 (SININOT01), 3255751R6 and 3255751T6 (OVARTUN01)	037241F1 (HUVENOB01), 1821492F6 (GBLATUT01), 2055814T6 (BEPINOT01), 2171401F6 and 2171401H1 (ENDCNOT03), 2668952F6 (ESOGTUT02), 3140313H1 and 3140313T6 (SMCCNOT02), 5031775H1 (EPIBTXT01)	187596R6 and 187596T6 (CARDNOT01), 919634R6 (RATRNOT02), 1992331H1 (CORPNOT02), 2062034H1 (OVARNOT03), 2212530F6 and 2212530H1 (SINTFET03), 2520479H1 (BRAITUT21), 2878284F6 (THYRNOT10), 2992354H1 (KIDNFET02), 4020719F6 (BRAXNOT02)	2253036H1 and 2253036R6 (OVARTUT01)
Library	LUNGNOT27	DENDTNT01	KIDNNOT26	BRSTNOT03	PANCNOT04	BRAITUT03	ENDCNOT03	SINTFET03	OVARTUT01
Clone ID	3475168	3836893	4072159	1003916	2093492	2108789	2171401	2212530	2253036
Nucleotide SEQ ID NO:	244	245	246	247	248	249	250	251	252
Protein SEQ ID NO:	011	111	112	113	114	115	911	211	118

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Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
611	253	2280161	PROSNON01	482326HI (HNTZRAT0I), 934345HI (CERVNOT0I), 1379358FI and 1379358TI (LUNGNOT10), 1438562TI (PANCNOT08), 1467511F6 (PANCTUT02), 1568138FI (UTRSNOT05), 1636106T6 (UTRSNOT06), 2134534F6 (ENDCNOT0I), 2280161HI and 2280161X19FI (PROSNON0I), 2789845F6 (COLNTUT16), 3096938HI (CERVNOT03), 3774621F6 (BRSTNOT25), 4222971HI (PANCNOT07), 5111983HI (ENDITXT0I), 5324177HI (FIBPFEN06)
120	254	2287485	BRAINON01	1454588F1 (PENITUT01), 1593332F6 (BRAINOT14), 2287485H1 and 2287485R6 (BRAINON01), 3765992H1 (BRSTNOT24), 4374293H1 (CONFNOT03), 4937931H1 (PROSTUS18), SBCA01722F1
121	255	2380344	ISLTNOT01	2380344F6 and 2380344HI (ISLTNOT01), 2888536T3 (LUNGFET04), SASA03644FI, SASA03689FI
122	256	2383171	ISLTNOT01	956296R1 (KIDNNOT05), 1342250F1 (COLNTUT03), 1468046F1 and 1468046T1 (PANCTUT02), 2383171H1 (ISLTNOT01), SBYA05452U1, SBYA01369U1
123	257	2396046	THP1AZT01	2396046F6, 2396046H1 and 2396118T6 (THP1AZT01)
124	258	2456587	ENDANOT01	2456587H1 and 2456587T6 (ENDANOT01), 2872569H1 (THYRNOT10), SBCA03778F1, SBDA00115F1, SBCA02401F1, SBCA03351F1, SBCA05164F1, SBCA04783F1, SBCA00155F1, SBCA04141F1
125	259	2484813	BONRTUT01	1234970T1 (LUNGFET03), 1338090F6 (COLNNOT13), 2484813H1 (BONRTUT01), SBCA00053F1, SBCA02064F1, SBCA02151F1, SBCA03770F1, SBCA04866F1, SBCA03406F1
126	260	2493851	ADRETUT05	2493851H1 (ADRETUT05), 3805916F6 (BLADTUT03), 4500439H1 and 4500748H1 (BRAVTXT02), 5120601H1 (SMCBUNT01)
127	261	2495719	ADRETUT05	603447RI (BRSTTUT01), 2495719HI (ADRETUT05), 2917493F6 (THYMFET03), 4647103HI (PROSTUT20), SBRA04984DI

				_			
Fragments	1833135R6 (BRAINON01), 1966515R6 (BRSTNOT04), 2331103R6 (COLNNOT11), 2614153H1 (GBLANOT01), 2656691F6 (LUNGTUT09), 3951176H1 (DRGCNOT01)	2655184HI (THYMNOT04), SBDA05215F1, SBDA05213F1, SBDA01516F1	1297974F1 and 1297974T6 (BRSTNOT07), 2630138F6 (COLNTUT15), 2848362H1 (BRSTTUT13)	1541617R1 and 1541617T1 (SINTTUT01), 2684504F6 and 2684504T6 (LUNGNOT23), 2796805H1 (NPOLNOT01), 2849906H1 (BRSTTUT13)	2899137H1 (DRGCNOT01), 3026490F6 and 3026490T6 (HEARFET02), 3483359H1 (KIDNNOT31)	1740227T6 (HIPONON01), 2986229H1 (CARGDIT01)	1754079F6 (LIVRTUT01), 3222081H1 (COLNNON03), 4053813T6 (SPLNNOT13), 4230282H1 (BRAMDIT01), SBDA07029F3
Library	GBLANOT01	THYMNOT04	BRSTTUT13	BRSTTUT13	DRGCNOT01	CARGDIT01	COLNNON03
Clone ID	2614153	2655184	2848362	2849906	2899137	2986229	3222081
Nucleotide SEQ ID NO:	262	263	264	265	266	267	268
Protein SEQ ID NO:	128	129	130	. 131	132	133	134

TABLE 2

	_		T							
Analytical Methods	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide
Identification										
Signature Sequences	MI - A21	MI - F28	MI - T18	MI - A29	MI - R24	MI - N21	M1 - Q20	M1 - A28	M1 - A29	MI - A29
Potential Glycosylation Sites				N58		N34	N100	N60		
Potential Phosphorylation Sites	T83 S38 T76	S30 S40 T47 T119 W125	170	S32 T64	T27 S39 S39 S44 S22 T27 S28 S57	T55 S30 S40 T55	S220 S70 S83 T131 S134 S141 T158 Y123	S62 T123 S142 S189 S62 T100 Y85	T48	
Amino Acid Residues	88	128	Ξ	011	78	88	227	198	65	154
Protein SEQ ID NO:	-	2	в	4	~ -87-	9	7	∞	6	01

TABLE 2 (cont.)

Analytical Methods	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM
Identification											
Signature Sequences	MI - A19	MI - G27	MI - A23	MI - T20	M88 - R112	MI - G19	M1-C19	MI - A21	M1 - C19	MI - G25	MI - G21
Potential Glycosylation Sites	N128	N166		N42 N47 N72 N207		N37		NI21 NI71			
Potential Phosphorylation Sites	T116 T26 T79 T85 T182 T188 T194 T206 S60 S123 S176 S213	T158 S128	S41	S49 T63 S92 T110 S127 T239	S43 S94 T114	S38 S43	T64 T67	S36 T58 T133 Y31	S76		S39 S53 S60
Amino Acid Residues	237	225	117	253	171	78	11	188	80	80	84
Protein SEQ ID NO:	=	12	13	14	15	91	17	18	19	20	21

TABLE 2 (cont.)

Analytical Methods	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide · HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM
Identification									·
Signature Sequences	M3 - A21	MI - C25	MI - A32	M1 - L29	MI - S18	MI - G34	M1 - E25	M1 - E29	MI - G20
Potential Glycosylation Sites		N97	N49 N91 N108 N128 N135 N190				N138 N206	N105	
Phosphorylation Sites	S41 T150	S3 S44 T75 S86 S183 S223 S36 S92 S205 Y40 Y110	T5 S76 T82 T93 T109 S121 T137 T170 S184 S11 T53 S75 S84 T132 S223 S274 Y69		S46 Y26		S93 S50 S167 S233 S89 T105 T214 S302 T318	S63	S21 S65 T93
Amino Acid Residues	171	243	311	57	82	115	327	133	129
Protein SEQ ID NO:	22	23	. 24	25	26	27	28	29	30

FABLE 2

Analytical Methods	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM
Identification										
Signature Sequences	MI - A21	MI - F28	MI - TI8	MI - A29	M1 - R24	MI - N21	MI - Q20	MI - A28	MI - A29	MI - A29
Potential Glycosylation Sites				N58		N34	N100	09N		
Potential Phosphorylation Sites	T83 S38 T76	S30 S40 T47 T119 W125	170	S32 T64	T27 S39 S39 S44 S22 T27 S28 S57	TSS S30 S40 TSS	S220 S70 S83 T131 S134 S141 T158 Y123	S62 T123 S142 S189 S62 T100 Y85	T48	
Amino Acid Residues	88	128	111	110	78	88	227	861	65	154
Protein SEQ ID NO:	-	2	3	4	\$	9	۲	8	6	01

TABLE 2 (cont.)

Analytical Methods	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM
Identification											
Signature Sequences	MI - A19	MI - G27	M1 - A23	M1 - T20	M88 - R112	MI - G19	MI - C19	MI - A21	MI - C19	MI - G25	MI - G21
Potential Glycosylation Sites	N128	N166		N42 N47 N72 N207		N37		N121 N171			
Potential Phosphorylation Sites	T116 T26 T79 T85 T182 T188 T194 T206 S60 S123 S176 S213	T158 S128	841	S49 T63 S92 T110 S127 T239	S43 S94 T114	S38 S43	T64 T67	S36 T58 T133 Y31	918		S39 S53 S60
Amino Acid Residues	237	225	117	253	171	78	11	188	80	80	84
Protein SEQ ID NO:	=	12	13	14	15	91	21	81	61	20	21

TABLE 2 (cont.)

Analytical Methods	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide . HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM
Identification									
Signature Sequences	M3 - A21	MI - C25	MI - A32	MI - L29	MI - S18	MI - G34	MI - E25	MI - E29	M1 - G20
Potential Glycosylation Sites		76N	N49 N91 N108 N128 N135 N190				N138 N206	N105	
Potential Phosphorylation Sites	S41 T150	S3 S44 T75 S86 S183 S223 S36 S92 S205 Y40 Y110	T5 S76 T82 T93 T109 S121 T137 T170 S184 S11 T53 S75 S84 T132 S223 S274 Y69		S46 Y26		S93 S50 S167 S233 S89 T105 T214 S302 T318	863	S21 S65 T93
Amino Acid Residues	171	243	311	57	82	115	327	133	129
Protein SEQ ID NO:	22	23	. 24	25	26	27	28	29	30

TABLE 2 (cont.)

Analytical Methods	Signal Peptide HMM BLAST - GenBank	Signal Peptide HMM	SPScan	Signal Peptide HMM	Signal Peptide HMM	SPScan	Signal Peptide HMM	Signal Peptide HMM
Identification	hematopoietic lineage switch 2 (g3169729)							
Signature Sequences	M1 - G20	MI-A18	M1 - G47	M9 - G40	MI-A19	MI - E34	MI - G28	MI - A21
Potential Glycosylation Sites	N61 N179 N353 N356 N396					N163 N184 N379		N46 N189 N382
Potential Phosphorylation Sites	S164 T32 S42 T141 T154 S155 T235 T262 T271 T334 T376 S402 S421 S435 T441 S19 S29 T327 S378	121	SS7 SS	T6 T14 T135	T15 S58 S66	T7 T76 S150 T224 S228 S257 S358 S474 S529 S539 T186 S219 S368 Y523	T80 S163	T47 T146 S233 S391 S403 T43 S130 S273 S339 S364
Amino Acid Residues	472	93	92	143	89	260	197	437
Protein SEQ ID NO:	31	. 32	33	34	35	36	37	38

Analytical Methods	Signal Peptide HMM	Signal Peptide HMM BLAST - GenBank	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM
Identification		receptor-activity-modifying protein (RAMP; g4165368)						
Signature Sequences	MI - G28	MI - R24	MI - V25	MI - S24	MI - T23	MI - G22	MI - G23	MI - P18
Potential Glycosylation Sites	N46 N64 N166 N191	N29 N58 N71 N103					N40	
Potential Phosphorylation Sites	S197 T49 T150 S193 T214 T215 T49 S111 S237	T73 S141	. 849	S89 S165 T174 T182 T83 S155	S54 S29 S98 S50 S57 T104	T29 S106 T120 S161 S195 S37 S47 T51 S136 S223 S230 S281	S21 T63 T63 A146	\$65
Amino Acid Residues	330	148	188	222	Ξ	341	148	87
Protein SEQ ID NO:	39	40	41	42	43	44	45	46

Identification Analytical Methods	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	putative involvement in cell wall Signal Peptide structure or biosynthesis (g3738170) HMM BLAST GenBank	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Cianal Dentide
						putative				
Signature Sequences	MI - P23	MI - L18	M1 - A20	MI - C21	MI - G18	MI - L25	M1 - A26	MI - G25	MI - A22	MI - P23
Potential Glycosylation Sites	N93 N207			N71		N250 N321 N463		N39		
Potential Phosphorylation Sites	T77 S95 S108 S280 S351 S121 S124 S153 T187	S25 S22	S62	T100 T73 S97 Y48	817 8110	S205 T31 S86 T236 S7 T447	T55 S34 S46 S69 T98 S108 T119 T167 S194 S2 S34 T153	S65 S36 T41 S51 S69 S81	S56	S29
Amino Acid Residues	383	109	185	110	126	488	197	84	64	140
Protein SEQ ID NO:	47	48	49	50	-95 -	52	53	54	\$\$	9\$

H			T T		ř –				
Analytical Methods	Signal Peptide HMM	Signal Peptide HMM BLAST - GENESEQ	Signal Peptide HMM	SPScan	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM	Signal Peptide HMM
Identification		3-acylating enzyme (Q44449)							
Signature Sequences	MI - A25	MI - G28	MI - C22	M55 - E848	MI - G18	MI - G27	M1 - G18	MI - G23	MI - A18
Potential Glycosylation Sites	N153	N190			N67			N53 N130 N289	
Potential Phosphorylation Sites	S53 S108 T216 S253 S277	S62 T166 S62 S71 Y246	S120 T154 T34 T37 S174	S98 T136 T67 S112 S234 S237	T68	T21 S117 S120	S107 S97 S146 S339 S440 S245 T303 S304 S399	T145 T214 T16 S24 S35 S45 T145 T269 S297 T300 T314 Y87	S38 S25 S75
Amino Acid Residues	285	262	189	257	82	202	450	322	104
Protein SEQ ID NO:	57	28	. 59	09	. 61	. 62	63	64	99

TABLE 2 (cont.)

Analytical Methods	SPscan HMM	SPscan HMM MOTIFS	SPScan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS
Identification			·				
Signature Sequences	MI through about S18 Transmembrane: MI through about Y17	M1 through about A24	M1 through about S31 Transmembrane: about M159 through about F178 about F109 through about S127 about F225 through about V243	MI through about S23 Transmembrane: MI through about L16	M1 through about Q18	M1 through about S25	MI through about G27
Potential Glycosylation Sites			N53	69N			
Potential Phosphorylation Sites		S23 S64	S392 S393 S31 S127 S179 S334 T338 S358 T383 Y323	859	S11 T26	S41 T79	S56
Amino Acid Residues	93	7.1	394	72	17	247	73
Protein SEQ ID NO:	99	29	~ 97-	69	70	12	72

- 97-

TABLE 2 (cont.)

SPscan HMM	SPscan HMM	can	ွှ				<u>}</u>
		SPScan	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS
M1 through about G20	M1 through about G30	M1 through about G26	M1 through about S19	M1 through about G27 Transmembrane: about W79 through about H97	M1 through about N34	M1 through about C18	M1 through about S30
					N48		
			T29 S46 T51	S62 S65		T33 R55	S34
70	<i>L</i> 9	16	98	112	54	57	52
73	74	75	76	77	78	79	08
	70	67	67	56 T29 S46 T51	74 67 75 91 76 \$6 T29 \$46 T51 77 112 \$62 \$65	73 70 74 67 75 91 76 56 T29 S46 T51 77 112 S62 S65 78 54 N48	73 70 70 74 67 75 91 76 56 T29 S46 T51 77 112 S62 S65 748 78 54 T33 R55

TABLE 2 (cont.)

Analytical Methods	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS
Identification							
Signature Sequences	MI through about S41	MI through about A31 Transmembrane: about L38 through about F55	MI through about E23	M1 through about A38 Transmembrane: about L23 through about T41	M1 through about K30 Microbodies C-terminal targetting signal: A65KV	M1 through about S29	M1 through about L19 Transmembrane: about 13 through about G20
Potential Glycosylation Sites				89 N95		N40	
Potential Phosphorylation Sites	T43 Y27	S45		6018 698	828	S29 S42 S46	S25 S46
Amino Acid Residues	64	65	56	120	67	62	75
Protein SEQ ID NO:			83	88	85	98	87

Analytical Methods	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPscan HMM MOTIFS	SPScan BLOCKS PRINTS MOTIFS	SPscan HMM	SPscan HMM MOTIFS
Identification							
Signature Sequences	M1 through about A20	M1 through about C48	MI through about G22	M1 through about P21	MI through about S18 Tyrosine specific protein phosphatases signature: about V328 through about F340	M1 through about S25	MI through about S22 Transmembrane: about V3 through about S21
Potential Glycosylation Sites					N226		
Potential Phosphorylation Sites	128	SII	838	S43	S415 S52 T77 S97 T178 T228 S282 S320 S332 S384 T401 T424 S483 S207 S230 S357 T410 Y263 Y365		839
Amino Acid Residues	80	90	116	29	538	88	611
Protein SEQ ID NO:		89	06.	16	2	93	94

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		T					-	
Analytical Methods	SPscan HMM MOTIFS	SPScan	Motifs BLOCKS BLAST	SPScan HMM Motifs	SPScan HMM Motifs BLAST	SPScan HMM Motifs	SPScan HMM Motifs	SPScan HMM Motifs
Identification								
Signature Sequences	MI through about G31 Transmembrane: about F108 through about L126	MI-S20	P116-V124 (urotensin II signature)	MI-S23, MI-S25	MI-A16, MI-S21 C40-C198 (cysteine spacing pattern similar to that of RoBo-1)	M1-A27	M1-S30, M1-G31	MI-A23, MI-L28
Potential Glycosylation Sites					N45 N73 N107 N118 N132 N172 N175 N185			
Potential Phosphorylation Sites	168	T115 T43 S91		S28 T70 S172 S25 S32 S48 S108 S131	SS5 S88 S121 S135	S36 S59 T143	T76 S64 Y103	S78 T4 T30 S130 S25 S29 T122
Amino Acid Residues	128	124		182	237	091	148	170
Protein SEQ ID NO:	95	96		-101	86	66	100	101

Analytical Methods	SPScan HMM Motifs	SPScan HMM Motifs	SPScan HMM Motifs	SPScan HMM Motifs	SPScan HMM Motifs	SPScan HMM Motifs	SPScan HMM Motifs	SPScan HMM Motifs
Identification								
Signature Sequences	MI-A26, MI-S28	MI-A25, MI-G26	MI-G18, MI-T25	MI-G22, MI-A20	MI-G26, MI-C25	MI-A22	MI-P19, MI-L22	MI-TIS, MI-P19
Potential Glycosylation Sites					N32 N101			N50
Potential Phosphorylation Sites	S50 S78 S91	T57 T80	T3	T29 S40 S72	T115 S38 T41	S53 S217 S240 S283 T224	S88 T73 S84	T82 S52 S77
Amino Acid Residues	150	142	110	120	135	301	103	95
Protein SEQ ID NO:	102	103	104	<u>S</u>	901	107	108	601

TABLE 2 (cont.)

Analytical Methods	SPScan HMM Motifs	SPScan HMM Motifs BLAST - GenBank	SPScan HMM Motifs	SPScan Motifs BLAST	SPScan	HMM Motifs	SPScan Motifs	HMM Motifs
Identification		NK cell activating receptor (g4493702)		Signal Peptide Containing Protein, Homology with KIAA0206	Signal Peptide Containing Protein	Signal Peptide Containing Protein	Signal Peptide Containing Protein	Signal Peptide Containing Protein
Signature Sequences	MI-P19, MI-A24	M1-A20	MI-G30, MI-G27	MI-G26 Signal Peptide	M1-Q29 Signal Peptide	M1-A20 Signal Peptide	M I-G23 Signal Peptide	MI-A24 Signal Peptide
Potential Glycosylation Sites		N146 N191 N194					N280 N384	N87
Potential Phosphorylation Sites	T84 S4	S179 S184 S51 T70 T158 S168 T228 Y29	S39 T61	SSI T46 S191		S29	S143 T156 T227 S235 T271 T293 T436 S453 S117 T148 T213 S263 S417 Y73	S19 S320 S69 S151 T171 T97 S393 Y193 Y378
Amino Acid Residues	113	234	611	200	225	155	468	403
Protein SEQ ID NO:	110	Ξ	112	113	114	115	911	117

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cal						
Analytical Methods	SPScan Motifs	SPScan Motifis HMM BLAST	SPScan Motifs	SPScan MotifS	SPScan Motifs BLAST	SPScan
Identification	Signal Peptide Containing Protein	Signal Peptide Containing Protein, Weakly similar to Putative Transmembrane Protein (PTM1) Precursor	Signal Peptide Containing Protein,	Signal Peptide Containing Protein	Signal Peptide Containing Protein, Weakly similar to OXA1L	Signal Peptide Containing Protein
Signature Sequences	M1-G25 Signal Peptide	M1-P21 Signal Peptide L226-W244, Y402-W422, V375-L392 and Y355-1376 Transmembrane Domains	M1-G24 Signal Peptide	M1-S15 Signal Peptide	M1-L25 Signal Peptide	M1-W16 Signal Peptide
Potential Glycosylation Sites	91 IN	N62 N79 N127 N157 N160	N100 N168 N319			
Potential Phosphorylation Sites	T131 S24 T79 T118 T123 T127	T176 S192 S196 T220 S344 S369 S476 T501 S529 S541 T548 T553 S48 S115 S121 T386 T424 S500	T457 T80 S86 T141 T372 T420 S447 S94 T102 S112 T240 S297 S353 S470	T46 S78 T12	S57 T320 S339 S396 S100 S239	
Amino Acid Residues	181	556	514	109	431	142
Protein SEQ ID NO:	811	611	120	121	122	123

TABLE 2 (cont.)

Analytical Methods	SPScan Motifs Pfam BLAST	SPScan Motifs	SPScan Motifs PROFILE- SCAN	SPScan Motifs BLAST Pfam PROFILE- SCAN	SPScan Motifs BLAST
Identification	Signal Peptide Containing Protein, Thrombospondin Type 1 Protein	Signal Peptide Containing Protein	Signal Peptide Containing Protein, Glycosyl Hydrolase Protein	Signal Peptide Containing Protein, Ribosomal Protein S18	Signal Peptide Containing Protein, Homology with GTP Binding Protein
Signature Sequences	MI-S28 Signal Peptide, D37-C81, W380-C437, W440- C492 and FS26-C583 Thrombospondin Type I Domains	M1-T19 Signal Peptide	M1-R32 Signal Peptide, V4-L53 Glycosyl Hydrolase Family 9 Active Site Signature	M1-S26 Signal Peptide, H79-H123 Ribosomal Protein S18 Signature	M1-S35 Signal Peptide
Potential Glycosylation Sites	N251	N322			N37 N92
Potential Phosphorylation Sites	T8 S28 S77 T169 T199 T235 S252 T320 S402 T413 S414 S558 S22 T25 S56 S62 S120 T184 S329 T423 S475 S574 Y226	S510 T24 T80 S91 T153 T165 S232 S248 S262 T300 T334 S380 S446 S16 T19 T60 S127 S273 T436 T531 S554 T564 Y135 Y489	T62 S27 T36	T105 T47 T56 S158	S112 S131
Amino Acid Residues	643	998	125	961	214
Protein SEQ ID NO:	124	-105-	126	127	128

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Analytical Methods	НММ	SPScan Motifs Pfam	SPScan Motifs	HMM Motifs BLOCKS PRINTS Pfam	SPScan Motifs Pfam	SPScan Motifs BLAST
Identification	Signal Peptide Containing Protein	Signal Peptide Containing Protein, Immunoglobulin Superfamily Protein	Signal Peptide Containing Protein	Signal Peptide Containing Protein, Adrenodoxin Family Iron-Sulfur Binding Protein, and Cytochrome C Family Heme Binding Protein	Signal Peptide Containing Protein, PF00646 F-Box Protein	Signal Peptide Containing Protein, F45G2.10 and Yhr122wp Homology
Signature Sequences	MI-S24 Signal Peptide	M1-A48 Signal Peptide, G59-S142 Immunoglobulin Domain	M1-A30 Signal Peptide	M1-W24 Signal Peptide, E131-K168 and C105-H115 Adrenodoxin Iron-Sulfur Binding Signature, C111-V116 Cytochrome C Heme Binding Signature, N69-A162 Iron-Sulfur Cluster Binding Domain	M1-G30 Signal Peptide, V28-L74 PF00646 F-Box Domain	M1-A27 Signal Peptide
Potential Glycosylation Sites		N50 N109				
Potential Phosphorylation Sites		S146 S179 S192 S239 S70 T126 T150	T176 T56 S72 S179 S256 S87	SII T41 T42 S83	893 T89 Y9	746 T55 S65 S124 T125 T46
Amino Acid Residues	88	260	295	183	113	160
Protein SEQ ID NO:	129	130	131	-106-	133	134

TABLE 3

Z IS	Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
	135	Hematopoietic/Immune (1.000)	Inflammation (1.000)	PBLUESCRIPT
	136	Hematopoietic/Immune (0.750) Cardiovascular (0.250)	Inflammation (0.750) Cancer (0.250)	pSPORTI
	137	Nervous (1.000)	Trauma (1.000)	pSPORTI
\Box	138	Musculoskeletal (1.000)	Inflammation (1.000)	pSPORT1
	139	Gastrointestinal (0.714) Cardiovascular (0.143) Reproductive (0.143)	Cancer (0.714) Trauma (0.143)	pSPORTI
	140	Nervous (1.000)	Neurological (0.500) Trauma (0.500)	pSPORTI
	141	Reproductive (0.293) Gastrointestinal (0.146) Hematopoietic/Immune (0.146)	Cancer (0.524) Inflammation (0.256) Fetal (0.146)	pSPORTI
07-	142	Reproductive (0.266) Gastrointestinal (0.170) Nervous (0.138)	Cancer (0.479) Inflammation (0.277) Fetal (0.181)	pINCY
	143	Reproductive (0.417) Nervous (0.292) Developmental (0.125)	Cancer (0.417) Inflammation (0.250) Fetal (0.167)	pINCY
	144	Reproductive (0.321) Cardiovascular (0.143) Developmental (0.143)	Cancer (0.464) Fetal (0.214) Inflammation (0.143)	pINCY
	145	Reproductive (0.600) Gastrointestinal (0.400)	Cancer (0.400) Trauma (0.400) Inflammation (0.200)	pINCY
	146	Cardiovascular (0.400) Dermatologic (0.200) Nervous (0.200)	Cancer (0.600) Fetal (0.600)	pINCY
	147	Developmental (0.667) Gastrointestinal (0.333)	Fetal (0.667) Cancer (0.333)	pINCY
	148	Reproductive (0.256) Nervous (0.248) Cardiovascular (0.137)	Cancer (0.479) Inflammation (0.214) Fetal (0.145)	pINCY
	149	Reproductive (0.244) Nervous (0.178) Hematopoietic/Immune (0.167)	Cancer (0.433) Inflammation (0.322) Fetal (0.156)	pINCY

Vector	t) pINCY	152) pINCY)) pINCY) pincy	(67) pINCY	(43) pINCY	pINCY) pincy) pincy	pSPORTI)) pincy	pincy (pincy (
Disease/Condition-Specific Expression (Total of Fraction)	Cancer (0.692) Fetal (0.154) Inflammation (0.154)	Cancer (0.494) Inflammation (0.278) Trauma (0.152)	Inflammation (0.371) Cancer (0.229) Fetal (0.200)	Cancer (0.549) Inflammation (0.176) Fetal (0.137)	Inflammation (0.667) Cancer (0.167) Trauma (0.167)	Inflammation (0.429) Cancer (0.286) Trauma (0.143)	Cancer (0.500) Inflammation (0.500)	Cancer (0.404) Inflammation (0.404) Fetal (0.212)	Cancer (0.415) Inflammation (0.358) Fetal (0.142)	Cancer (1.000)	Fetal (0.500) Inflammation (0.250) Trauma (0.250)	Cancer (0.583) Fetal (0.292) Inflammation (0.250)	Cancer (0.735) Inflammation (0.176) Fetal (0.029)
Tissue Expression (Fraction of Total)	Cardiovascular (0.923) Developmental (0.077)	Reproductive (0.215) Nervous (0.190) Gastrointestinal (0.177)	Reproductive (0.200) Nervous (0.171) Hematopoietic/Immune (0.143)	Reproductive (0.333) Nervous (0.157) Hematopoietic/Immune (0.137)	Gastrointestinal (0.500) Urologic (0.167)	Gastrointestinal (0.429) Reproductive (0.286) Nervous (0.143)	Reproductive (1.000)	Hematopoietic/Immune (0.346) Reproductive (0.154) Gastrointestinal (0.115)	Reproductive (0.236) Hematopoietic/Immune (0.217) Gastrointestinal (0.132)	Gastrointestinal (1.000)	Developmental (0.500) Hematopoietic/Immune (0.250) Nervous (0.250)	Hematopoietic/Immune (0.250) Reproductive (0.250) Nervous (0.208)	Gastrointestinal (0.412) Reproductive (0.412)
Nucleotide SEQ ID NO:	150	151	152	153	154	155	156	157	158	159	160	191	162

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TABLE 3 (cont.)

TABLE 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
175	Reproductive (0.444) Developmental (0.167) Cardiovascular (0.111)	Cancer (0.556) Fetal (0.278) Trauma (0.111)	pSPORT1
176	Reproductive (0.294) Gastrointestinal (0.176) Cardiovascular (0.118)	Cancer (0.765) Fetal (0.118) Inflammation (0.118)	pSPORTI
177	Gastrointestinal (1.000)	Cancer (0.667) Inflammation (0.333)	pINCY
178	Reproductive (0.385) Nervous (0.231) Gastrointestinal (0.154)	Cancer (0.385) Inflammation (0.385)	pINCY
179	Reproductive (0.500) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.667) Fetal (0.167) Inflammation (0.167)	PBLUESCRIPT
180	Cardiovascular (0.231) Reproductive (0.231) Gastrointestinal (0.154)	Cancer (0.615) Inflammation (0.308) Fetal (0.154)	pINCY
181	Reproductive (0.324) Gastrointestinal (0.176) Cardiovascular (0.130)	Cancer (0.519) Inflammation (0.222) Fetal (0.157)	pINCY
182	Reproductive (0.320) Nervous (0.180) Gastrointestinal (0.120)	Cancer (0.580) Inflammation (0.160) Fetal (0.100)	pINCY
183	Gastrointestinal (0.667) Reproductive (0.333)	Cancer (1.000)	pINCY
184	Urologic (0.667) Dermatologic (0.333)	Cancer (0.667) Fetal (0.333)	pSPORTI
185	Cardiovascular (0.500) Reproductive (0.500)	Cancer (1.000)	pINCY
186	Reproductive (0.393) Developmental (0.107) Urologic (0.107)	Cancer (0.607) Fetal (0.179) Inflammation (0.107)	pINCY
187	Cardiovascular (0.400) Reproductive (0.333) Gastrointestinal (0.133)	Inflammation (0.467) Cancer (0.267) Fetal (0.267)	pSPORT1
188	Nervous (0.318) Reproductive (0.227) Urologic (0.136)	Cancer (0.636) Inflammation (0.136) Trauma (0.091)	pINCY

SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
189	Cardiovascular (0.500) Reproductive (0.500)	Cancer (1.000)	pINCY
061	Reproductive (0.318) Nervous (0.227) Hematopoietic/Immune (0.136)	Cancer (0.500) Fetal (0.227) Inflammation (0.227)	pINCY
161	Reproductive (0.253) Cardiovascular (0.158) Gastrointestinal (0.147)	Cancer (0.463) Inflammation (0.232) Fetal (0.200)	pINCY
192	Reproductive (0.333) Gastrointestinal (0.286) Cardiovascular (0.095)	Cancer (0.571) Inflammation (0.333) Fetal (0.095)	pINCY
193	Reproductive (0.304) Cardiovascular (0.217) Gastrointestinal (0.130)	Cancer (0.435) Inflammation (0.391) Fetal (0.174)	pINCY
194	Reproductive (0.312) Nervous (0.188) Cardiovascular (0.125)	Cancer (0.438) Inflammation (0.250) Fetal (0.188)	pINCY
195	Developmental (1.000)	Fetal (1.000)	pINCY
961	Reproductive (0.233) Cardiovascular (0.209) Nervous (0.140)	Cancer (0.605) Fetal (0.186) Inflammation (0.116)	pINCY
197	Reproductive (0.182) Gastrointestinal (0.136) Hematopoietic/Immune (0.136)	Cancer (0.477) Inflammation (0.341) Fetal (0.182)	pINCY
198	Gastrointestinal (0.205) Reproductive (0.205) Cardiovascular (0.114)	Inflammation (0.341) Cancer (0.250) Fetal (0.227)	pINCY
199	Cardiovascular (0.520) Reproductive (0.280) Developmental (0.160)	Cancer (0.720) Fetal (0.200) Inflammation (0.080)	pINCY
200	Lung (0.958) Developmental (0.25) Musculoskeletal (0.042)	Cancer (0.583) Fetal or Proliferating (0.292) Inflammation (0.167)	PBLUESCRIPT
201	Reproductive (0.571) Musculoskeletal (0.143) Nervous (0.143) Urologic (0.143)	Cancer (0.429) Inflammation (0.571)	pSPORTI

Endocrine (0.250) Nervous (0.250) Cardiovascular (0.125) Developmental (0.125) Gastrointestinal (0.125) Reproductive (0.125) 204 Lung (1.000) 205 Cardiovascular (0.231) Dermatologic (0.231) Reproductive (0.231) 206 Nervous (0.596) Reproductive (0.154) Castrointestinal (0.077) 207 Gastrointestinal (1.000) 208 Reproductive (0.300) Hematopoietic/Immune (0.200) Nervous (0.150) 210 Nervous (0.625) Reproductive (0.250) Musculoskeletal (0.125) 211 Nervous (0.261) Reproductive (0.304) 212 Testis (1.000) 214 Reproductive (0.476) Gastrointestinal (0.286) Cardiovascular (0.095)		Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
203 Lung (1.000) Fetal or Proliferating (1.000) 204 Lung (0.500) Penis (0.500) Cancer (0.500) 205 Cardiovascular (0.231) Dermatologic (0.231) Fetal or Proliferating (0.385) Cancer (0.308) 206 Reproductive (0.231) Cancer (0.442) Neurological (0.192) 207 Gastrointestinal (0.077) Inflammation (0.231) 208 Reproductive (0.300) Hematopoietic/Immune (0.200) Cancer (0.450) Inflammation (0.400) 209 Heart (0.500) Brain (0.500) Neurological (0.500) Inflammation (0.500) 210 Nervous (0.521) Reproductive (0.364) Cancer (0.730) Fetal or Proliferating (0.250) 211 Nervous (0.521) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174) 212 Testis (1.000) Inflammation (1.000) 213 Nervous (0.400) Reproductive (0.400) Cancer (0.522) Fetal or Proliferating (0.174) 214 Reproductive (0.476) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286) 214 Reproductive (0.476) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286)		202	Endocrine (0.250) Nervous (0.250) Cardiovascular (0.125) Developmental (0.125) Gastrointestinal (0.125) Reproductive (0.125)	Cancer (0.375) Inflammation (0.625) Fetal or Proliferating (0.125)	pSPORTI
204 Lung (0.500) Penis (0.500) Cancer (0.500) 205 Cardiovascular (0.231) Dermatologic (0.231) Fetal or Proliferating (0.385) Cancer (0.308) 206 Reproductive (0.231) Dermatologic (0.231) Cancer (0.442) Neurological (0.192) 207 Gastrointestinal (1.0007) Inflammation (1.000) 208 Reproductive (0.300) Hematopoietic/Immune (0.200) Cancer (0.450) Inflammation (0.400) 209 Heart (0.500) Brain (0.500) Nervous (0.150) 210 Nervous (0.625) Reproductive (0.304) Neurological (0.500) Inflammation (0.500) 211 Nervous (0.261) Reproductive (0.304) Cancer (0.450) Fetal or Proliferating (0.174) 212 Testis (1.000) Inflammation (1.000) 213 Nervous (0.400) Reproductive (0.400) 214 Reproductive (0.476) Gastrointestinal (0.286) 214 Reproductive (0.476) Gastrointestinal (0.286) 214 Reproductive (0.406) Cancer (0.410) Inflammation (0.286)		203	Lung (1.000)	Fetal or Proliferating (1.000)	pINCY
205 Cardiovascular (0.231) Dermatologic (0.231) Fetal or Proliferating (0.385) Cancer (0.308) 206 Nervous (0.236) Reproductive (0.154) Cancer (0.442) Neurological (0.192) 207 Gastrointestinal (0.077) Inflammation (0.231) 208 Reproductive (0.300) Hematopoietic/Immune (0.200) Cancer (0.450) Inflammation (0.400) 209 Heart (0.500) Brain (0.500) Neurological (0.500) Inflammation (0.500) 210 Nervous (0.625) Reproductive (0.250) Cancer (0.750) Fetal or Proliferating (0.250) 211 Nervous (0.625) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174) 212 Testis (1.000) Inflammation (1.000) 213 Nervous (0.400) Reproductive (0.400) Cancer (0.400) Inflammation (0.400) 214 Reproductive (0.406) Reproductive (0.406) Cancer (0.400) Inflammation (0.200) 214 Reproductive (0.406) Reproductive (0.406) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286)	I	204	Lung (0.500) Penis (0.500)	Cancer (0.500)	pINCY
Nervous (0.596) Reproductive (0.154) Cancer (0.442) Neurological (0.192) Inflammation (0.231) Inflammation (0.231) Inflammation (1.000) Reproductive (0.300) Hematopoietic/Immune (0.200) Fetal or Proliferating (0.250) Nervous (0.150) Nervous (0.150) Nervous (0.625) Reproductive (0.250) Neurological (0.500) Inflammation (0.500) Nervous (0.261) Reproductive (0.250) Neurological (0.125) Neurological (0.125) Neurological (0.125) Neurological (0.125) Inflammation (0.130) Inflammation (0.130) Inflammation (0.130) Nervous (0.400) Reproductive (0.400) Neurological (0.200) Neurological (0.000) Neurol		205		Fetal or Proliferating (0.385) Cancer (0.308)	pINCY
207 Gastrointestinal (1.000) Inflammation (1.000) Inflammation (1.000) 208 Reproductive (0.300) Hematopoietic/Immune (0.200) Cancer (0.450) Inflammation (0.400) Fetal or Proliferating (0.250) 209 Heart (0.500) Brain (0.500) Neurological (0.500) Inflammation (0.500) Cancer (0.750) Fetal or Proliferating (0.250) 210 Nervous (0.625) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174) 211 Nervous (0.261) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174) 212 Testis (1.000) Inflammation (0.130) 213 Nervous (0.400) Reproductive (0.400) Cancer (0.400) Inflammation (0.400) 214 Reproductive (0.476) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286) 214 Reproductive (0.476) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286)		206	Nervous (0.596) Reproductive (0.154) Gastrointestinal (0.077)	Cancer (0.442) Neurological (0.192) Inflammation (0.231)	pINCY
208 Reproductive (0.300) Hematopoietic/Immune (0.200) Cancer (0.450) Inflammation (0.400) 209 Heart (0.500) Brain (0.500) Neurological (0.500) Inflammation (0.500) 210 Nervous (0.625) Reproductive (0.250) Cancer (0.750) Fetal or Proliferating (0.250) 211 Nervous (0.261) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174) 212 Testis (1.000) Inflammation (1.000) 213 Nervous (0.400) Reproductive (0.400) Cancer (0.400) Inflammation (0.400) 214 Reproductive (0.476) Gastrointestinal (0.200) Cancer (0.714) Inflammation (0.286) 214 Reproductive (0.476) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286)		207	Gastrointestinal (1.000)	Inflammation (1.000)	pINCY
Heart (0.500) Brain (0.500) Neurological (0.500) Inflammation (0.500) Nervous (0.625) Reproductive (0.250) Cancer (0.750) Fetal or Proliferating (0.250) Musculoskeletal (0.125) Neurological (0.125) Nervous (0.261) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174) Testis (1.000) Inflammation (0.130) Nervous (0.400) Reproductive (0.400) Cancer (0.400) Inflammation (0.400) Reproductive (0.476) Gastrointestinal (0.200) Cancer (0.714) Inflammation (0.286) Reproductive (0.476) Gastrointestinal (0.095) Cancer (0.714) Inflammation (0.286)		208	Reproductive (0.300) Hematopoietic/Immune (0.200) Nervous (0.150)	Cancer (0.450) Inflammation (0.400) Fetal or Proliferating (0.250)	pSPORTI
Nervous (0.625) Reproductive (0.250) Cancer (0.750) Fetal or Proliferating (0.250) Musculoskeletal (0.125) Neurological (0.125) Nervous (0.261) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174) Testis (1.000) Inflammation (0.130) Nervous (0.400) Reproductive (0.400) Cancer (0.400) Inflammation (0.400) Reproductive (0.476) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286) Reproductive (0.995) Cancer (0.714) Inflammation (0.286)		209	Heart (0.500) Brain (0.500)	Neurological (0.500) Inflammation (0.500)	pINCY
Nervous (0.261) Reproductive (0.304) Cancer (0.522) Fetal or Proliferating (0.174)		210	Nervous (0.625) Reproductive (0.250) Musculoskeletal (0.125)	Cancer (0.750) Fetal or Proliferating (0.250) Neurological (0.125)	pINCY
Testis (1.000) Inflammation (1.000) Nervous (0.400) Reproductive (0.400) Cancer (0.400) Inflammation (0.400) Neurological (0.200) Reproductive (0.476) Gastrointestinal (0.286) Cancer (0.714) Inflammation (0.286) Neurological (0.048) Neurological (0.048) Cancer (0.95) Cancer (0.95) Cancer (0.986) Cancer	l	211	Nervous (0.261) Reproductive (0.304) Gastrointestinal (0.174)	Cancer (0.522) Fetal or Proliferating (0.174) Inflammation (0.130)	pSPORTI
Nervous (0.400) Reproductive (0.400) Cancer (0.400) Inflammation (0.400) Gastrointestinal (0.200) Neurological (0.200) Reproductive (0.476) Gastrointestinal (0.286) Neurological (0.048) Cardiovascular (0.095) Neurological (0.048)		212	Testis (1.000)	Inflammation (1.000)	PBLUESCRIPT
Reproductive (0.476) Gastrointestinal (0.286) Cardiovascular (0.095) Neurological (0.048)		213	Nervous (0.400) Reproductive (0.400) Gastrointestinal (0.200)	Cancer (0.400) Inflammation (0.400) Neurological (0.200)	PBLUESCRIPT
				Cancer (0.714) Inflammation (0.286) Neurological (0.048)	pSPORTI

	Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
	215	Reproductive (0.284) Gastrointestinal (0.216) Nervous (0.176) Hematopoietic/Immune (0.108) Cardiovascular (0.108)	Cancer (0.486) Inflammation (0.351) Fetal or Proliferating (0.122)	pSPORTI
	216	Uterus (0.500) Prostate (0.500)	Cancer (0.500) Inflammation (0.500)	pINCY
	217	Nervous (0.429) Cardiovascular (0.143) Gastrointestinal (0.143) Hematopoietic/Immune (0.143) Reproductive (0.143)	Cancer (0.571) Inflammation (0.429) Fetal or Proliferating (0.285)	pSPORTI
	218	Reproductive (0.450) Hematopoietic/Immune (0.200) Nervous (0.100) Gastrointestinal (0.100)	Cancer (0.650) Inflammation (0.200) Fetal or Proliferating (0.050)	pINCY
-11	219	Reproductive (0.364) Cardiovascular (0.182) Nervous (0.182)	Cancer (0.636) Fetal or Proliferating (0.182)	pINCY
3-	220	Prostate (1.000)	Inflammation (1.000)	pSPORTI
	221	Developmental (0.333) Nervous (0.333) Reproductive (0.333)	Cancer (0.667) Fetal or Proliferating (0.667)	pSPORTI
	222	Reproductive (0.393) Hematopoietic/Immune (0.180) Nervous (0.098) Cardiovascular (0.098)	Cancer (0.508) Inflammation (0.344) Fetal or Proliferating (0.066)	pSPORTI
	223	Endocrine (0.333) Gastrointestinal (0.333) Reproductive (0.333)	Cancer (1.000)	pINCY
	224	Cardiovascular (0.200) Developmental (0.200) Gastrointestinal (0.200) Reproductive (0.200) Urologic (0.200)	Cancer (0.800) Fetal or Proliferating (0.200)	pINCY
	225	Lung (1.000)	Cancer (1.000)	pINCY
	226	Reproductive (0.302) Hematopoietic/Immune (0.254) Cardiovascular (0.111)	Cancer (0.381) Inflammation (0.381) Fetal or Proliferating (0.286)	pSPORTI

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Vector	pINCY	pINCY	pINCY	PBLUESCRIPT	PINCY	PINCY	pINCY	pINCY	pINCY	pINCY	pINCY	pINCY	pINCY
Disease/Condition-Specific Expression (Total of Fraction)	Inflammation (1.000)	Cancer (0.656) Inflammation (0.250) Fetal or Proliferating (0.094)	Cancer (0.500) Fetal or Proliferating (0.167) Inflammation (0.333)	Cell Proliferation (0.500) Inflammation (0.500)	Cancer (0.500) Cell Proliferation (0.333) Inflammation (0.167)	Cancer (0.500) Inflammation (0.500)	Cancer (0.456) Inflammation (0.235) Trauma (0.147)	Cancer (0.545) Inflammation (0.255) Trauma (0.109)	Cancer (0.538) Inflammation (0.231) Trauma (0.154)	Cancer (1.000)	Cancer (0.571) Cell Proliferation (0.143) Trauma (0.143)	Cancer (0.453) Inflammation (0.241) Cell Proliferation (0.175)	Trauma (0.333) Cancer (0.167) Cell Proliferation (0.167)
Tissue Expression (Fraction of Total)	Lymphocytes (1.000)	Cardiovascular (0.531) Reproductive (0.250) Urologic (0.094)	Reproductive (0.333) Cardiovascular (0.167) Gastrointestinal (0.167) Endocrine (0.167) Hematopoietic/Immune (0.167)	Hematopoietic/Immune (0.500) Reproductive (0.500)	Cardiovascular (0.333) Nervous (0.333) Developmental (0.167)	Gastrointestinal (0.938) Reproductive (0.062)	Nervous (0.324) Reproductive (0.235) Hematopoietic/Immune (0.118)	Nervous (0.255) Reproductive (0.255) Musculoskeletal (0.182)	Musculoskeletal (0.308) Reproductive (0.231) Gastrointestinal (0.154)	Nervous (1.000)	Gastrointestinal (0.429) Hematopoietic/Immune (0.143) Nervous (0.143)	Reproductive (0.254) Gastrointestinal (0.160) Nervous (0.128)	Nervous (0.333) Dermatologic (0.167) Endocrine (0.167)
Nucleotide SEQ ID NO:	227	228	229	· 230	231	232	233	234	235	236	237	238	239

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
240	Nervous (0.273) Reproductive (0.227) Endocrine (0.136)	Cancer (0.545) Cell Proliferation (0.182) Inflammation (0.182)	pINCY
241	Reproductive (0.273) Hematopoietic/Immune (0.182) Urologic (0.182)	Cancer (0.455) Cell Proliferation (0.273) Inflammation (0.273)	pINCY
242	Endocrine (1.000)	Trauma (1.000)	pSPORTI
243	Reproductive (1.000)	Cancer (1.000)	pINCY
244	Hematopoietic/Immune (0.545) Musculoskeletal (0.182) Cardiovascular (0.091)	Inflammation (0.636) Trauma (0.182) Cancer (0.091)	pINCY
245	Hematopoietic/Immune (0.400) Musculoskeletal (0.300) Cardiovascular (0.150)	Inflammation (0.650) Cancer (0.300)	pINCY
246	Urologic (1.000)	Cancer (0.500) Cell Proliferation (0.500)	pINCY
247	Nervous (0.292) Reproductive (0.222) Musculoskeletal (0.125)	Cell Proliferation (0.625) Inflammation/Trauma (0.181)	pSPORTI
248	Reproductive (0.211) Developmental (0.132) Nervous (0.132)	Cell Proliferation (0.658) Inflammation/Trauma (0.184)	pSPORTI
249	Nervous (0.500) Gastrointestinal (0.300) Hematopoietic/Immune (0.100)	Cell Proliferation (0.900) Inflammation/Trauma (0.300)	pSPORT1
250	Cardiovascular (0.209) Gastrointestinal (0.140) Hematopoietic/Immune (0.140)	Cell Proliferation (0.605) Inflammation/Trauma (0.256)	pINCY
251	Nervous (0.308) Cardiovascular (0.154) Gastrointestinal (0.154)	Cell Proliferation (0.616) Inflammation/Trauma (0.269)	pINCY
252	Reproductive (1.000)	Cell Proliferation (1.000)	pSPORTI

<u> </u>	Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
	253	Reproductive (0.324) Nervous (0.162) Gastrointestinal (0.113)	Cell Proliferation (0.641) Inflammation/Trauma (0.197)	pSPORTI
	254	Reproductive (0.315) Nervous (0.296) Developmental (0.093)	Cell Proliferation (0.630) Inflammation/Trauma (0.278)	pSPORTI
	255	Nervous (0.211) Reproductive (0.211) Gastrointestinal (0.158)	Cell Proliferation (0.579) Inflammation/Trauma (0.298)	pINCY
	. 256	Reproductive (0.250) Gastrointestinal (0.148) Hematopoietic/Immune (0.148)	Cell Proliferation (0.705) Inflammation/Trauma (0.193)	pINCY
	257	Hematopoietic/Immune (1.000)	Cell Proliferation (0.400) Inflammation/Trauma (0.600)	pINCY
-116-	258	Cardiovascular (0.333) Reproductive (0.333) Developmental (0.167)	Cell Proliferation (0.833) Inflammation/Trauma (0.333)	PBLUESCRIPT
	259	Cardiovascular (0.333) Reproductive (0.250) Developmental (0.167)	Cell Proliferation (0.625) Inflammation/Trauma (0.208)	pINCY
	260	Endocrine (0.500) Cardiovascular (0.250) Nervous (0.250)	Cell Proliferation (0.750) Inflammation/Trauma (0.500)	pINCY
	261	Reproductive (0.252) Cardiovascular (0.155) Hematopoietic/Immune (0.136)	Cell Proliferation (0.728) Inflammation/Trauma (0.194)	pINCY
<u> </u>	262	Reproductive (0.274) Cardiovascular (0.177) Nervous (0.145)	Cell Proliferation (0.742) Inflammation/Trauma (0.210)	pINCY
	263	Reproductive (0.267) Cardiovascular (0.160) Hematopoietic/Immune (0.127)	Cell Proliferation (0.654) Inflammation/Trauma (0.193)	piNCY
	264	Nervous (0.229) Hematopoietic/Immune (0.200) Reproductive (0.200)	Cell Proliferation (0.743) Inflammation/Trauma (0.286)	pINCY
	265	Hematopoietic/Immune (0.333) Gastrointestinal (0.167) Nervous (0.133)	Cell Proliferation (0.600) Inflammation/Trauma (0.333)	pINCY .

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease/Condition-Specific Expression (Total of Fraction)	Vector
266	Nervous (0.290) Reproductive (0.258) Cardiovascular (0.129)	Cell Proliferation (0.677) Inflammation/Trauma (0.194)	pINCY
267	Reproductive (0.261) Hematopoietic/Immune (0.217) Cardiovascular (0.087)	Cell Proliferation (0.652) Inflammation/Trauma (0.391)	pINCY
268	Gastrointestinal (0.227) Reproductive (0.193) Hematopoietic/Immune (0.168)	Cell Proliferation (0.731) Inflammation/Trauma (0.227)	pSPORTI

TABLE 4

Polynucleotide SEQ ID NO:	Clone ID	Library	Library Description
135	443531	MPHGNOT03	The library was constructed using RNA isolated from plastic adherent mononuclear cells isolated from buffy coat units obtained from unrelated male and female donors.
136	632860	NEUTGMT01	The library was constructed using RNA isolated from peripheral blood granulocytes collected by density gradient centrifugation through Ficoll-Hypaque. The cells were isolated from buffy coat units obtained from 20 unrelated male and female donors. Cells were cultured in 10 nM GM-CSF for I hour before washing and harvesting for RNA preparation.
. 137	010019	CRBLNOT01	The library was constructed using RNA isolated from the cerebellum tissue of a 69-year-old Caucasian male who died from chronic obstructive pulmonary disease. Patient history included myocardial infarction, hypertension, and osteoarthritis.
138	726498	SYNOOAT01	The library was constructed using RNA isolated from the knee synovial membrane tissue of an 82-year-old female with osteoarthritis.
139	795064	OVARNOT03	The library was constructed using RNA isolated from ovarian tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology for the associated tumor tissue indicated grade 2 mucinous cystadenocarcinoma. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, cerebrovascular disease, breast cancer, and uterine cancer.
140	924925	BRAINOT04	The library was constructed using RNA isolated from the brain tissue of a 44-year-old Caucasian male with a cerebral hemorrhage. The tissue, which contained coagulated blood, came from the choroid plexus of the right anterior temporal lobe. Family history included coronary artery disease and myocardial infarction.

Polynucleotide SEQ ID NO:	Clone ID	Library	Library Description
141	962390	BRSTTUT03	The library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
. 142	1259405	MENITUT03	The library was constructed using RNA isolated from brain meningioma tissue removed from a 35-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a benign neoplasm in the right cerebellopontine angle of the brain. Patient history included hypothyroidism. Family history included myocardial infarction and breast cancer.
143	1297384	BRSTNOT07	The library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, atherosclerotic coronary artery disease, and type II diabetes.
144	1299627	BRSTNOT07	The library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, atherosclerotic coronary artery disease, and type II diabetes.
145	1306026	PLACNOT02	The library was constructed using RNA isolated from the placental tissue of a Hispanic female fetus, who was prematurely delivered at 21 weeks' gestation. Serologies of the mother's blood were positive for CMV (cytomegalovirus).

ucleotide Clone ID Library Library Description	1316219 BLADTUT02 The library was constructed using RNA isolated from bladder tumor tissue removed from an 80-year-old Caucasian female during a radical cystectomy and lymph node excision. Pathology indicated grade 3 invasive transitional cell carcinoma. Family history included osteoarthritis and atherosclerosis.	1329031 PANCNOT07 The library was constructed using RNA isolated from the pancreatic tissue of a Caucasian male fetus, who died at 23 weeks' gestation.	1483050 CORPNOT02 The library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.	1514160 PANCTUT01 The library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Family history included cardiovascular disease, type II diabetes, and stomach cancer.	1603403 LUNGNOT15 The library was constructed using RNA isolated from lung tissue removed from a 69-year-old Caucasian male during a segmental lung resection. Pathology for the associated tumor tissue indicated residual grade 3 invasive squamous cell carcinoma. Patient history included acute myocardial infarction, prostatic hyperplasia, and malignant skin neoplasm. Family history included cerebrovascular disease, type I diabetes, acute myocardial infarction, and arteriosclerotic coronary disease.	1652303 PROSTUT08 The library was constructed using RNA isolated from prostate tumor tissue removed from a 60-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated an adenocarcinoma (Gleason grade 3+4). Adenofibromatous hyperplasia was also present. The patient presented with elevated prostate specific antigen (PSA). Patient history included a kidney cyst. Family history included tuberculosis, cerebrovascular disease, and arteriosclerotic
Polynucleotide SEQ ID NO:	146	147	. 148	149	150	151

Library Description	The library was constructed using RNA isolated from diseased colon tissue removed from a 16-year-old Caucasian male during a total colectomy with abdominal/perineal resection. Pathology indicated gastritis and pancolonitis consistent with the acute phase of ulcerative colitis. There was only mild involvement of the ascending and sigmoid colon, and no significant involvement of the cecum, rectum, or terminal ileum. Family history included irritable bowel syndrome.	The library was constructed using RNA isolated from duodenal tissue of a 8-year-old Caucasian female, who died from head trauma. Serology was positive for cytomegalovirus (CMV).	The library was constructed using RNA isolated from colon tissue removed from a 56-year-old Caucasian female with Crohn's disease during a partial resection of the small intestine. Pathology indicated Crohn's disease of the ileum and ileal-colonic anastomosis, causing a fistula at the anastomotic site that extended into pericolonic fat. The ileal mucosa showed linear and puncture ulcers with intervening normal tissue. Previous surgeries included a partial ileal resection and permanent ileostomy. Family history included irritable bowel syndrome.	The library was constructed using RNA isolated from stomach tumor tissue obtained from a 68-year-old Caucasian female during a partial gastrectomy. Pathology indicated a malignant lymphoma of diffuse large-cell type. Patient history included thalassemia. Family history included acute leukemia, malignant neoplasm of the esophagus, malignant stomach neoplasm, and atherosclerotic coronary artery disease.	The library was constructed using RNA isolated from diseased prostate tissue removed from a 65-year-old Caucasian male during a radical prostatectomy. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma.	The library was constructed using 1 microgram of polyA RNA isolated from THP-1 promonocyte cells treated for three days with 0.8 micromolar 5-aza-2'-deoxycytidine. THP-1 (ATCC TIB 202) is a human promonocyte line derived from peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.
Library	COLNNOT23	DUODNOT02	COLNNOT22	STOMTUT02	PROSNOT20	THPIAZT0I
Clone ID	1693358	1707111	1738735	1749147	1817722	1831290
Polynucleotide SEQ ID NO:	152	153	-121-	155	156	157

area of the skull of a 30-year-old Caucasian female. Pathology indicated chondroid chordoma with neoplastic cells reactive for keratin. 171 COLNNOT16 The library was constructed using RNA isolated from sigmoid colon tissue removed from a 62-year-old Caucasian male during a sigmoidectomy and permanent colostomy.
172 1032647 0011111111111111111111111111111111111

Library Description	The library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, atherosclerotic coronary artery disease, and type II diabetes.	The library was constructed using RNA isolated from ovarian tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology for the associated tumor tissue indicated grade 2 mucinous cystadenocarcinoma. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, cerebrovascular disease, breast cancer, and uterine cancer.	The library was constructed and normalized from 4.4 million independent clones from the PROSNOT11 library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male who died from a gunshot wound. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization period.	The library was constructed and normalized from 4.88 million independent clones from the BRAINOT03 library. Starting RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.	The library was constructed using RNA isolated from diseased sigmoid colon tissue obtained from a 70-year-old Caucasian male during colectomy with permanent ileostomy. Pathology indicated chronic ulcerative colitis. Patient history included benign neoplasm of the colon. Family history included atherosclerotic coronary artery disease and myocardial infarctions	The library was constructed using RNA isolated from adrenal tissue removed from a 61-year-old female during a bilateral adrenalectomy. Patient history included an unspecified disorder of the adrenal glands.
Library	BRSTNOT07	OVARNOT03	PROSNON01	BRAINONOI	COLSUCT01	ADRENOT07
Clone ID	2124245	2132626	2280639	2292356	2349310	2373227
Polynucleotide SEQ ID NO:	173		-124-	176	7.1	178

-124-

Library Description	The library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.	The library was constructed using RNA isolated from an aortic smooth muscle cell line derived from the explanted heart of a male during a heart transplant.	The library was constructed using RNA isolated from sigmoid mesentery tumor tissue obtained from a 61-year-old female during a total abdominal hysterectomy and bilateral salpingooophorectomy with regional lymph node excision. Pathology indicated a metastatic grade 4 malignant mixed mullerian tumor present in the sigmoid mesentery at two sites.	The library was constructed using RNA isolated from rib tumor tissue removed from a 16-year-old Caucasian male during a rib osteotomy and a wedge resection of the lung. Pathology indicated a metastatic grade 3 (of 4) osteosarcoma, forming a mass involving the chest wall.	The library was constructed using RNA isolated from ovarian tumor tissue removed from a 51-year-old Caucasian female during an exploratory laparotomy, total abdominal hysterectomy, salpingo-oophorectomy, and an incidental appendectomy. Pathology indicated mucinous cystadenoma presenting as a multiloculated neoplasm involving the entire left ovary. The right ovary contained a follicular cyst and a hemorrhagic corpus luteum. The uterus showed proliferative endometrium and a single intramural leiomyoma. The peritoneal biopsy indicated benign glandular inclusions consistent with endosalpingiosis. Family history included atherosclerotic coronary artery disease, benign hypertension, breast cancer, and uterine cancer.	The library was constructed using RNA isolated from epidermal breast keratinocytes (NHEK). NHEK (Clontech #CC-2501) is a human breast keratinocyte cell line derived from a 30-year-old black female during breast-reduction surgery.
Library	ENDANOT01	SMCANOT01	CONUTUT01	BONRTUT01	OVARTUT02	KERANOT02
Clone ID	2457682	2480426	2503743	2537684	2593853	2622354
Polynucleotide SEQ ID NO:	6/1	180		182	183	184

Library Description	LUNGTUT08 The library was constructed using RNA isolated from lung tumor tissue removed from a 63-year-old Caucasian male during a right upper lobectomy with fiberoptic bronchoscopy. Pathology indicated a grade 3 adenocarcinoma. Patient history included atherosclerotic coronary artery disease, an acute myocardial infarction, rectal cancer, an asymptomatic abdominal aortic aneurysm, and cardiac dysrhythmia. Family history included congestive heart failure, stomach cancer, and lung cancer, type II diabetes, atherosclerotic coronary artery disease, and an acute myocardial infarction.	KIDNNOT19 The library was constructed using RNA isolated from kidney tissue removed a 65-year-old Caucasian male during an exploratory laparotomy and nephroureterectomy. Pathology for the associated tumor tissue indicated a grade 1 renal cell carcinoma within the upper pole of the left kidney. Patient history included malignant melanoma of the abdominal skin, benign neoplasm of colon, cerebrovascular disease, and umbilical hernia. Family history included myocardial infarction, atherosclerotic coronary artery disease, cerebrovascular disease, prostate cancer, myocardial infarction, and atherosclerotic coronary artery disease.	THP1AZS08 The subtracted THP-1 promonocyte cell line library was constructed using 5.76 million clones from a 5-aza-2'-deoxycytidine (AZT) treated THP-1 cell library. Starting RNA was made from THP-1 promonocyte cells treated for three days with 0.8 micromolar AZT. The library was oligo(dT)-primed, and cDNAs were cloned directionally into the pSPORT1 vectoring system using Sal1 (5') and Notl (3'). The hybridization probe for subtraction was derived from a similarly constructed library, made from 1 microgram of polyA RNA isolated from untreated THP-1 cells. 5.76 million clones from the AZ-treated THP-1 cell library were then subjected to two rounds of subtractive hybridization with 5 million clones from the untreated THP-1 cell library. Subtractive hybridization conditions were based on the methodologies of Swaroop et al. (Nucl. Acids Res. (1991) 19:1954) and Bonaldo et al. (Genome Res (1996) 6: 791-806).	BRSTNOT12 The library was constructed using RNA isolated from diseased breast tissue removed from a 32-year-old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated nonproliferative fibrocystic disease. Family history included benign hypertension and
Clone ID	2641377	2674857	2758485	2763296
Polynucleotide Clone ID SEQ ID NO:	185 2641377	186 2674857	2758485	2763296

Polynucleotide SEQ ID NO:	Clone ID	Library	Library Description
189	2779436	OVARTUT03	The library was constructed using RNA isolated from ovarian tumor tissue removed from the left ovary of a 52-year-old mixed ethnicity female during a total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal and lymphatic structure biopsy, regional lymph node excision, and peritoneal tissue destruction. Pathology indicated an invasive grade 3 (of 4) scroanaplastic carcinoma forming a mass in the left ovary. The endometrium was atrophic. Multiple (2) leiomyomata were identified, one subserosal and 1 intramural. Pathology also indicated a metastatic grade 3 seroanaplastic carcinoma involving the omentum, cul-de-sac peritoneum, left broad ligament peritoneum, and mesentery colon. Patient history included breast cancer, chronic peptic ulcer, and joint pain. Family history included colon cancer, cerebrovascular disease, breast cancer, type II diabetes, esophagus cancer, and depressive disorder.
190	2808528	BLADTUT08	The library was constructed using RNA isolated from bladder tumor tissue removed from a 72-year-old Caucasian male during a radical cystectomy and prostatectomy. Pathology indicated an invasive grade 3 (of 3) transitional cell carcinoma in the right bladder base. Family history included myocardial infarction, cerebrovascular disease, brain cancer, and myocardial infarction.
191	2809230	BLADTUT08	The library was constructed using RNA isolated from bladder tumor tissue removed from a 72-year-old Caucasian male during a radical cystectomy and prostatectomy. Pathology indicated an invasive grade 3 (of 3) transitional cell carcinoma in the right bladder base. Patient history included pure hypercholesterolemia and tobacco abuse. Family history included myocardial infarction, cerebrovascular disease, brain cancer, and myocardial infarction.
192	2816821	BRSTNOT14	The library was constructed using RNA isolated from breast tissue removed from a 62-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated an invasive grade 3 (of 4), nuclear grade 3 (of 3) adenocarcinoma, ductal type. Ductal carcinoma in situ, comedo type, comprised 60% of the tumor mass. Metastatic adenocarcinoma was identified in one (of 14) axillary lymph nodes with no perinodal extension. The tumor cells were strongly positive for estrogen receptors and weakly positive for progesterone receptors. Patient history included a benign colon neoplasm, hyperlipidemia, and cardiac dysrhythmia. Family history included atherosclerotic coronary artery disease, myocardial infarction, colon cancer.

Library Description	The library was constructed using RNA isolated from breast tissue removed from a 62-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated an invasive grade 3 (of 4), nuclear grade 3 (of 3) adenocarcinoma, ductal type. Ductal carcinoma in situ, comedo type, comprised 60% of the tumor mass. Metastatic adenocarcinoma was identified in one (of 14) axillary lymph nodes with no perinodal extension. The tumor cells were strongly positive for estrogen receptors and weakly positive for progesterone receptors. Patient history included a benign colon neoplasm, hyperlipidemia, and cardiac dysrhythmia. Family history included atherosclerotic coronary artery disease, myocardial infarction, colon cancer, ovarian cancer, lung cancer, and cerebrovascular disease.	The library was constructed using RNA isolated from diseased ileum tissue obtained from a 26-year-old Caucasian male during a partial colectomy, permanent colostomy, and an incidental appendectomy. Pathology indicated moderately to severely active Crohn's disease. Family history included enteritis of the small intestine.	The library was constructed using RNA isolated from kidney tissue removed from a Caucasian female fetus, who died at 17 weeks' gestation from anencephalus.	The library was constructed using RNA isolated from kidney tissue removed from a Caucasian male fetus, who was stillborn with a hypoplastic left heart and died at 23 weeks' gestation.	The library was constructed using RNA isolated from kidney tissue removed from a Caucasian male felus, who was stillborn with a hypoplastic left heart and died at 23 weeks' gestation.	The library was constructed using RNA isolated from right coronary and right circumflex coronary artery tissue removed from the explanted heart of a 46-year-old Caucasian male during a heart transplantation. Patient history included myocardial infarction from total occlusion of the left anterior descending coronary artery, atherosclerotic coronary artery disease, hyperlipidemia, myocardial ischemia, dilated cardiomyopathy, and left ventricular dysfunction. Previous surgeries included cardiac catheterization. Family history included atherosclerotic coronary artery disease.
Library	BRSTNOT14	SININOT04	KIDNFET01	KIDNFET02	KIDNFET02	HEAANOT01
Clone ID	2817268	2923165	2949822	2992192	2992458	3044710
Polynucleotide SEQ ID NO:		194	561	961	<i>L</i> 61	198

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LUNO 10113 In the library was constructed using RNA isolated from tumorous lung tissue removed from the right upper lobe of a 47-year-old Caucasian male during a segmental lung resection. Pathology indicated invasive grade 3 (of 4) adenocarcinoma. Family history included atherosclerotic coronary artery disease, and type II diabetes.
LUNGNOT01 The library was constructed at Stratagene using RNA isolated from the lung tissue of a 72-year-old male.
CRBLNOT01 The library was constructed using RNA isolated from the cerebellum tissue of a 69-year-old Caucasian male who died from chronic obstructive pulmonary disease. Patient history included myocardial infarction, hypertension, and osteoarthritis.
PRAITUTOI The library was constructed using RNA isolated from brain tumor tissue removed from a 50-year-old Caucasian female during a frontal lobectomy. Pathology indicated recurrent grade 3 oligoastrocytoma with focal necrosis and extensive calcification. Patient history included a speech disturbance and epilepsy. The patient's brain had also been irradiated with a total dose of 5,082 cyg (Fraction 8). Family history included a brain tumor.
LUNGFET03 The library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus who died at 20 weeks' gestation.
Caucasian male during a segmental lung resection and regional lymph node resection. Pathology indicated fibrosis pleura was puckered, but not invaded. Pathology for the associated tumor tissue indicated an invasive pulmonary grade 3 adenocarcinoma. Patient history included cerebrovascular disease, arteriosclerotic coronary artery disease, thrombophlebitis, chronic obstructive pulmonary disease, and asthma. Family history included intracranial hematoma, cerebrovascular disease, arteriosclerotic coronary artery disease, and type I diabetes.

Polynucleotide SEQ ID NO:	Clone ID	Library	Library Description
205	1450703	PENITUTOI	The library was constructed using RNA isolated from tumor tissue removed from the penis of a 64-year-old Caucasian male during penile amputation. Pathology indicated a fungating invasive grade 4 squamous cell carcinoma involving the inner wall of the foreskin and extending onto the glans penis. Patient history included benign neoplasm of the large bowel, atherosclerotic coronary artery disease, angina pectoris, gout, and obesity. Family history included malignant pharyngeal neoplasm, chronic lymphocytic leukemia, and chronic liver disease.
. 206	1910668	CONNTUT01	The library was constructed using RNA isolated from a soft tissue tumor removed from the clival area of the skull of a 30-year-old Caucasian female. Pathology indicated chondroid chordoma with neoplastic cells reactive for keratin.
207	1955143	CONNNOT01	The library was constructed using RNA isolated from mesentery fat tissue obtained from a 71-year-old Caucasian male during a partial colectomy and permanent colostomy. Family history included atherosclerotic coronary artery disease, myocardial infarction, and extrinsic asthma.
208	1961637	BRSTNOT04	The library was constructed using RNA isolated from breast tissue removed from a 62-year-old East Indian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated an invasive grade 3 ductal carcinoma. Patient history included benign hypertension, hyperlipidemia, and hematuria. Family history included cerebrovascular and cardiovascular disease, hyperlipidemia, and liver cancer.
209	1990762	CORPNOT02	The library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
210	1994131	CORPNOT02	The library was constructed using RNA isolated from diseased corpus callosum tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.

- 7	Clone ID	Library	Library Description
	1997745	BRSTTUT03	The library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
	2009035	TESTNOT03	The library was constructed using polyA RNA isolated from testicular tissue removed from a 37-year-old Caucasian male who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
ł	2009152	TESTNOT03	The library was constructed using polyA RNA isolated from testicular tissue removed from a 37-year-old Caucasian male who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
	2061752	OVARNOT03	The library was constructed using RNA isolated from ovarian tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology for the associated tumor tissue indicated grade 2 mucinous cystadenocarcinoma. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, stress reaction, cerebrovascular disease, breast cancer, and uterine cancer.
	2061933	OVARNOT03	The library was constructed using RNA isolated from ovarian tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology for the associated tumor tissue indicated grade 2 mucinous cystadenocarcinoma. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, stress reaction, cerebrovascular disease, breast cancer, and uterine cancer.

Library Library Description	UTRSNOT08 The library was constructed using RNA isolated from uterine tissue removed from a 35-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. Pathology indicated that the endometrium was secretory phase with a benign endometrial polyp 1 cm in diameter. The cervix showed mild chronic cervicitis. Family history included atherosclerotic coronary artery disease and type II diabetes.	BRAITUT02 The library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypemephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.	PRSTNOTO7 The library was constructed using RNA isolated from diseased breast tissue removed from a 43- year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.	PANCTUT02 The library was constructed using RNA isolated from pancreatic tumor tissue removed from a 45-year-old Caucasian female during radical pancreaticoduodenectomy. Pathology indicated a grade 4 anaplastic carcinoma. Family history included benign hypertension, hyperlipidemia and atherosclerotic coronary artery disease.	PROSNON01 This normalized prostate library was constructed from 4.4 M independent clones from the PROSNOT11 library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male who died from a self-inflicted gunshot wound. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232,
Clone ID	2081422	2101278	2121353	2241736	2271935
Polynucleotide SEQ ID NO:	216	. 217	218	219	220

-132-

Library Description	The library was constructed using RNA isolated from breast tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated multicentric invasive grade 4 lobular carcinoma. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular and cardiovascular disease, breast and prostate cancer, and type I diabetes.	The library was constructed using RNA isolated from breast tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated multicentric invasive grade 4 lobular carcinoma. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular and cardiovascular disease, breast and prostate cancer, and type I diabetes.	The library was constructed RNA isolated from adrenal tumor tissue removed from a 52-year-old Caucasian female during a unilateral adrenalectomy. Pathology indicated a pheochromocytoma.	The library was constructed using RNA isolated from lung tumor tissue removed from the right lower lobe a 57-year-old Caucasian male during a segmental lung resection. Pathology indicated an infiltrating grade 4 squamous cell carcinoma. Multiple intrapulmonary peribronchial lymph nodes showed metastatic squamous cell carcinoma. Patient history included a benign brain neoplasm and tobacco abuse. Family history included spinal cord cancer, type II diabetes, cerebrovascular disease, and malignant prostate neoplasm.	The library was constructed using RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma and a metastatic tumor. Patient history included type II diabetes, thyroid disorder, depressive disorder, hynerlinidemia esonhageal ulcer and tabascouse.
Library	BRSTNOT05	BRSTNOT05	ADRETUT05	LUNGTUTII	LUNGTUT09
Clone ID	2295344	2303994	2497805	2646362	2657146
Polynucleotide SEQ ID NO:	221	222	223	224	225

Polymucleotide Clone ID Library This subtracted THP-1 promoncoye cell ine library was constructed using 5.76 million clones from a 5-aza-2-deoxycyldine (A2) treated THP-1 cell fibrary. Starting RNA was made from THP-1 promoncoye cell ine library was constructed using 5.76 million clones from a 5-aza-2-deoxycyldine (A2) treated THP-1 cell fibrary. Starting RNA was made from THP-1 promoncoye cell ine library was the mach collected from a millary constructed therapy, made from RNA isolated from murtaned THP-1 promoncoye cell inerapy care then cell library were then unablicated from memorisal library librar				T			-	
Clone ID 2755786 2831245 T 3116250 L 3129630 L 1236968 L 1334153 CC	Library Description	This subtracted THP-1 promonocyte cell line library was constructed using 5.76 million clones from a 5-aza-2'-deoxycytidine (AZ) treated THP-1 cell library. Starting RNA was made from THF 1 promonocyte cells treated for three days with 0.8 micromolar AZ. The hybridization probe for subtraction was derived from a similarly constructed library, made from RNA isolated from untreated THP-1 cells. 5.76 million clones from the AZ-treated THP-1 cell library were then subjected to two rounds of subtractive hybridization with 5 million clones from the untreated THP cell library. Subtractive hybridization conditions were based on the methodologies of Swaroop et al., NAR (1991) 19:1954, and Bonaldo et al., Genome Research (1996) 6:791. THP-1 (ATCC TIB 202) is a human promonocyte line derived from peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.	The library was constructed using RNA isolated from nonactivated Th1 cells. These cells were differentiated from umbilical cord CD4 T cells with IL-12 and B7-transfected COS cells.	The library was constructed using RNA isolated from tumorous lung tissue removed from the right upper lobe of a 47-year-old Caucasian male during a segmental lung resection. Pathology indicated invasive grade 3 (of 4) adenocarcinoma. Family history included atherosclerotic coronary artery disease, and type II diabetes.	The library was constructed using RNA isolated from tumorous lung tissue removed from a 70-year-old Caucasian female during a lung lobectomy of the left upper lobe. Pathology indicated grade 3 (of 4) adenocarcinoma and vascular invasion. Patient history included tobacco abuse, depressive disorder, anxiety state, and skin cancer. Family history included cerebrovascular disease, congestive heart failure.	The library was constructed using RNA isolated from the HMC-1 human mast cell line derived from a 52-year-old female. Patient history included mast cell lankamin	The library was constructed using RNA isolated from lung tissue removed from a Caucasian female fetus who died at 20 weeks' pestation	The library was constructed using RNA isolated from ascending colon tissue of a 28-year-old
3 8 8 13 13 13 13 13 13 13 13 13 13 13 13 13	Library	THP1AZS08	TLYMNOT03	LUNGTUTI3	LUNGTUT12	HMC1NOT01	LUNGFET03	COLNNOTI3
Polymucleotide SEQ ID NO: 226 227 228 230 231 231	Clone ID	2755786	2831245	3116250	3129630	007632	1236968	1334153
	Polynucleotide SEQ ID NO:		227	228	229	230	231	232

Polynucleotide Clone ID Library The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of creebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionerosis. Patienth history included cerebrovascular disease and malignant prostate neoplasm. The library was constructed using RNA isolated from ileum tissue removed from a 18-year-old Caucasian female during obovel anasonomis. Pathology indicated Crohns disease of the lieum. Pathology in facility from a 18-year-old Caucasian male during a segmental lung resection and bronchoscopy. This itssue was constructed using RNA isolated from lymph node tissue removed from a 67-year-old Caucasian male during a segmental lung resection and bronchoscopy. This itssue was classively frectoric with 10% viable tumor. Pathology for the associated tumor tissue indicated invasive grade 3-4 squamous cell carcinoma. Patient history included management and bronchoscopy. The ilbrary was constructed using RNA isolated from lymph node tissue removed from a 67-year-old Caucasian male during a segmental lung resection and bronchoscopy. This ilstace was constructed using RNA isolated from prostate tumor tissue indicated invasive grade 3-4 squamous cell carcinoma. Patient history included hung repolasm, and benigh hyperteals prostatectomy, and unionary diversion, and benigh hyperteal during a radical prostatectomy, radical cystectomy, and unionary diversion, and benigh hyperteal grade 3 transitional cell carcinoma. Patient history included from a 45-year-old Caucasian male during a radical prostate from prostate tumor tissue removed from a 45-year-old caucasian male during unidated standovastictomy. Pathology indicated grade 3 transitional cell carcinoma. Patient history included from a 45-year-old caucasian male during indicated grade 3 transitional rell carcinoma. Patient history included mumor tissue indicated invasive muchan patent grade 2-3 adenoca						
1396975 1501749 1575240 L	Library Description	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of cerebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionecrosis. Patient history included cerebrovascular disease, deficiency anemia, hyperlipidemia, epilepsy, and tobacco use. Family history included cerebrovascular disease and malignant prostate neoplasm.	The library was constructed using RNA isolated from ileum tissue removed from an 18-year-old Caucasian female during bowel anastomosis. Pathology indicated Crohn's disease of the ileum. Family history included cerebrovascular disease and atherosclerotic coronary artery disease.	The library was constructed using RNA isolated from lymph node tissue removed from a 67-year-old Caucasian male during a segmental lung resection and bronchoscopy. This tissue was extensively necrotic with 10% viable tumor. Pathology for the associated tumor tissue indicated invasive grade 3-4 squamous cell carcinoma. Patient history included hemangioma. Family history included atherosclerotic coronary artery disease, benign hypertension, and consessive hear failure	The library was constructed using RNA isolated from prostate tumor tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology indicated grade 3 transitional cell carcinoma. Patient history included lung neoplasm, and benign hypertension. Family history included malignant breast neoplasm, tuberculosis, cerebrovascular disease, atherosclerotic coronary aftery disease, and lung cancer.	The library was constructed using RNA isolated from breast tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated invasive nuclear grade 2-3 adenocarcinoma. Patient history included valvuloplasty of mitral valve and rheumatic heart disease. Family history included cardiovascular disease and true II dispense
	Library	BRAITUT08	SINTBST01	LNODNOT03	PROSTUT09	BRSTNOT09
Polymucleotide SEQ 1D NO: 233 235 235 236	Clone ID	1396975	1501749	1575240	1647884	1661144
	Polynucleotide SEQ ID NO:	233	234	235	236	237

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Library Description	The library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.	The library was constructed using RNA isolated from breast tumor tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology indicated invasive nuclear grade 2-3 adenocarcinoma. Patient history included valvuloplasty of mitral valve and rheumatic heart disease. Family history included cardiovascular disease and type II diabetes.	The library was constructed using RNA isolated from breast tissue removed from a 62-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated an invasive grade 3 (of 4), nuclear grade 3 (of 3) adenocarcinoma. Patient history included a benign colon neoplasm, hyperlipidemia, cardiac dysrhythmia, and obesity. Family history included cardiovascular and cerebrovascular disease and colon, ovary and lung cancer.	The library was constructed using RNA isolated from kidney tissue removed a 65-year-old Caucasian male during an exploratory laparotomy and nephroureterectomy. Pathology for the associated tumor tissue indicated grade 1 renal cell carcinoma within the upper pole of the left kidney. Patient history included malignant melanoma of the abdominal skin, benign neoplasm of colon, cerebrovascular disease, and umbilical hemia. Family history included myocardial infarction, atherosclerotic coronary artery disease, cerebrovascular disease, and prostate cancer	The normalized adrenal gland library was constructed from 1.36 x 1e6 independent clones from an adrenal tissue library. Starting RNA was made from adrenal gland tissue removed from a 20-year-old Caucasian male who died from head trauma. The library was normalized in two rounds using conditions adapted from Soares et al. (PNAS (1994) 91:9228-9232) and Bonaldo et al. (Genome Res (1996) 6: 791-806) using a significantly longer (48-hours/round) reannealing hybridization
Library	PROSNOTIS	BRSTTUT08	BRSTNOT14	KIDNNOT19	ADRENON04
Clone ID	1685409	1731419	2650265	2677129	3151073
Polynucleotide SEQ ID NO:	238	239	240	241	242
			<u></u>		

Polynucleotide SEQ ID NO:	Clone ID	Library	Library Description
243	3170095	BRSTNOT18	The library was constructed using RNA isolated from diseased breast tissue removed from a 57-year-old Caucasian female during a unilateral simple extended mastectomy. Pathology indicated mildly proliferative breast disease. Patient history included breast cancer and osteoarthritis. Family history included type II diabetes, gallbladder and breast cancer, and chronic lymphocytic leukemia.
244	3475168	LUNGNOT27	The library was constructed using RNA isolated from lung tissue removed from a 17-year-old Hispanic female.
245	3836893	DENDTNT01	The library was constructed using RNA isolated from treated dendritic cells from peripheral blood.
246	4072159	KIDNNOT26	The library was constructed using RNA isolated from left kidney medulla and cortex tissue removed from a 53-year-old Caucasian female during a nephroureterectomy. Pathology for the associated tumor tissue indicated grade 2 renal cell carcinoma involving the lower pole of the kidney. Patient history included hyperlipidemia, cardiac dysrhythmia, menorrhagia, cerebrovascular disease, atherosclerotic coronary artery disease, and tobacco abuse. Family history included cerebrovascular disease and atherosclerotic coronary artery disease.
247	1003916	BRSTNOT03	The library was constructed using RNA isolated from diseased breast tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy. Pathology for the associated tumor tissue indicated residual invasive grade 3 mammary ductal adenocarcinoma. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia and a malignant neoplasm of the colon.
248	2093492	PANCNOT04	The library was constructed using RNA isolated from the pancreatic tissue of a 5-year-old Caucasian male who died in a motor vehicle accident.
249	2108789	BRAITUT03	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe a 17-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a grade 4 fibrillary giant and small-cell astrocytoma. Family history included benign hypertension and cerebrovascular disease.
250	2171401	ENDCNOT03	The library was constructed using RNA isolated from dermal microvascular endothelial cells removed from a neonatal Caucasian male.

Library Description	The library was constructed using RNA isolated from small intestine tissue removed from a Caucasian female fetus, who died at 20 weeks' gestation.	The library was constructed using RNA isolated from ovarian tumor tissue removed from a 43-year-old Caucasian female during removal of the fallopian tubes and ovaries. Pathology indicated grade 2 mucinous cystadenocarcinoma involving the entire left ovary. Patient history included mitral valve disorder, pneumonia, and viral hepatitis. Family history included atherosclerotic coronary artery disease, pancreatic cancer, stress reaction, cerebrovascular disease, breast cancer, and uterine cancer.	The normalized prostate library was constructed from 4.4 M independent clones from the PROSNOT11 library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male who died from a self-inflicted gunshot wound. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization period.	The library was constructed and normalized from 4.88 million independent clones from the BRAINOT03 library. RNA was made from brain tissue removed from a 26-year-old Caucasian male during cranioplasty and excision of a cerebral meningeal lesion. Pathology for the associated tumor tissue indicated a grade 4 oligoastrocytoma in the right fronto-parietal part of the brain.	The library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.	The library was constructed using RNA isolated from a pooled collection of pancreatic islet cells.	The library was constructed using RNA isolated from THP-1 promonocyte cells treated for three days with 0.8 micromolar 5-aza-2'-deoxycytidine. THP-1 (ATCC TIB 202) is a human promonocyte line derived from peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.	The library was constructed using RNA isolated from aortic endothelial cell tissue from an explanted heart removed from a male during a heart transplant.
Library	SINTFET03	OVARTUT01	PROSNON01	BRAINON01	ISLTNOT01	ISLTNOT01	THP1AZT01	ENDANOTOI
Clone 1D	2212530	2253036	2280161	2287485	2380344	2383171	2396046	2456587
Polynucleotide SEQ ID NO:	251	252	253	254	255	256	257	258

Polynucleotide SEQ ID NO:	Clone ID	Library	Library Description
259	2484813	BONRTUT01	The library was constructed using RNA isolated from rib tumor tissue removed from a 16-year-old Caucasian male during a rib osteotomy and a wedge resection of the lung. Pathology indicated a metastatic grade 3 (of 4) osteosarcoma, forming a mass involving the chest wall.
260	2493851	ADRETUT05	The library was constructed RNA isolated from adrenal tumor tissue removed from a 52-year-old Caucasian female during a unilateral adrenalectomy. Pathology indicated a pheochromocytoma.
261	2495719	ADRETUT05	The library was constructed RNA isolated from adrenal tumor tissue removed from a 52-year-old Caucasian female during a unilateral adrenalectomy. Pathology indicated a pheochromocytoma.
262	2614153	GBLANOT01	The library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension.
263	2655184	THYMNOT04	The library was constructed using RNA isolated from thymus tissue removed from a 3-year-old Caucasian male, who died from anoxia. Serologies were negative. The patient was not taking any medications.
264	2848362	BRSTTUT13	The library was constructed using RNA isolated from breast tumor tissue removed from the right breast of a 46-year-old Caucasian female during a unilateral extended simple mastectomy with breast reconstruction. Pathology indicated an invasive grade 3 adenocarcinoma, ductal type with apocrine features and greater than 50% intraductal component. Patient history included breast cancer.
265	2849906	BRSTTUT13	The library was constructed using RNA isolated from breast tumor tissue removed from the right breast of a 46-year-old Caucasian female during a unilateral extended simple mastectomy with breast reconstruction. Pathology indicated an invasive grade 3 adenocarcinoma, ductal type with apocrine features and greater than 50% intraductal component. Patient history included breast cancer.

Library Description	The library was constructed using RNA isolated from dorsal root ganglion tissue removed from the cervical spine of a 32-year-old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus, infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy. Surgeries included colonoscopy, large intestine biopsy, adenotonsillectomy, and nasopharyngeal endoscopy and biopsy; treatment included radiation therapy.	The library was constructed using RNA isolated from diseased cartilage tissue. Patient history included osteoarthritis.	The normalized colon library was constructed from 2.84x10° independent clones from the COLNNOT07 library. Starting RNA was made from colon tissue removed from a 60-year-old Caucasian male during a left hemicolectomy. The normalization and hybridization conditions were adapted from Soares et al. (PNAS (1994) 91:9228-9232), Swaroop et al. (Nucl. Acids Res. (1991) 19:1954) and Bonaldo et al. (Genome Res (1996) 6: 791-806), using a significantly longer (48 hour) reannealing hybridization period.
Library	DRGCNOT01	CARGDIT01	COLNNON03
Clone ID	2899137	2986229	3222081
Polynucleotide SEQ ID NO:	266	. 267	268

Table :

Parameter Threshold		Mismatch <50%		ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity- 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and Probability value= 1.0E-3 or less	Score=10-50 bits, depending on individual protein families
Reference	Perkin-Elmer Applied Biosystems, Foster City, CA.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Perkin-Elmer Applied Biosystems, Foster City, CA.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.
Description	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	A program that assembles nucleic acid sequences.	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS and PRINTS databases to search for gene families, sequence homology, and structural fingerprint regions.	A Hidden Markov Models-based application useful for protein family search.
Program	ABI FACTURA	ABI/PARACEL FDF	ABI AutoAssembler	BLAST	FASTA	BLIMPS	PFAM

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Score≃ 4.0 or greater
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186- 194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length≂ 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <u>supra;</u> Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, W1.	

TABLE 6

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Nucleotide of
SEQ ID NO:		SEQ ID NO	Fragment	Fragment
		443531HI		253
		1406807F6	152	336
135	443531	443531T6	847	355
		SBBA00451F1	396	856
		SBBA00676F1	546	865
		632860HI	13	253
136	632860	784715R3	17	999
		509590H1	455	706
137	670010	1H0100L9		263
		669971R1		633
		726498H1	13	263
138	726498	726498R6	13	489
		866599R3	7	099
		795064H1	98	323
		4339458H1	4	284
139	795064	937605R3	98	505
		2381151F6	592	1057
		1466346F6	857	1241
		924925H1		412
140	924925	3268330HI	2	239
		759120R3	==	629
		1907958F6		478
141	962390	023569F1	1122	470
		167282F1	1216	543
		1309211F1	911	1224

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Ctontine Nucleotide of	TO
SEO ID NO:		SEO ID NO	Kraemont	Enuing Indefeorate of
		1750405111	717 A Z	riagment on
		111001071	2	117
		Z4/Z4Z5HI	331	354
		774303R1	061	743
142	1259405	1520779F1	418	1001
		1693833F6	914	1467
		1831858T6.comp	1336	1742
		1527737T6.comp	1386	1829
		1297384HI	402	641
		1269310F6	-	492
143	1297384	1457367F1	792	1380
		415587R1	1358	1712
		SANA02967F1	1143	614
		1299627H1		250
		1359140F6	1004	1573
144	1299621	1349224F1	1330	1731
		SBAA01431F1	46	397
	-	SBAA02909F1	898	262
		SBAA01156F1	106	1266
		1306026H1		223
145	1306026	1464088R6	302	829
		SBAA02496F1	92	568
		SBAA04305F1	366	883
,		1316219H1	246	491
146	1316219	2458603F6	_	402
		2504756T6	086	380
		1329031H1	_	264
147	1329031	1329031T6	505	
		1329031F6	-	523

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Fuding Nucleotide of
SEQ ID NO:		SEQ ID NO	Fragment	Fragment
		1483050H1	722	931
		855049H1	_	267
		077017F1	6901	629
148	1483050	1483050F6	722	1215
		1480024T6	2063	1315
		1483050T6	2068	1535
		759486R1	1762	2089
		IS14160H1	1640	1838
		1866765T7	2383	2210
		782676R1	1652	1875
149	1514160	008055X4	0601	1804
		008055X5	1316	1952
		1866765F6	2209	2391
		SAOA03127F1	2129	1703
		1603403H1	7	224
150	1603403	372910F1	420	44
		733299R7	219	420
		1652303H1	4	256
		1671806H1		224
		1341743T1	2069	0061
		3803812H1	389	269
151	1652303	1878546F6	747	1344
		1428640F1	1081	1664
		2058609R6	1715	2098
		1331621F1	1780	2096
		1306331T1	1897	2098

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Marshouth of	1
SEQ ID NO:		SEQ ID NO	Fragment	Fragment	
		1693358HI	41	125	1
		2498265HII	: 	250	
152	1693358	1867125F6	205	373	
		1693358T6	1094	416	
		2245848R6	737	1103	
		1707711HI	408	626	1
		1484609T1	2165	1855	
		1707711F6	408	286	
153	170711	1267959F1	1721	2182	
		1484609F1	1855	2178	
		SAJA00930F1	544	1132	
		SAJA01300R1	1675	1212	
		SAJA00999R1	1675	1142	
· ·		1738735HI	7	236	
154	1738735	SAJA00944R1	393	' 'S	
	_	SAJA00137F1	913	685	
		SAJA03629F1	435	42	
155		1749147H1		276	1
155	1749147	1749147F6	47	457	
155		1749147T6	479		
156	1817722	1817722H1		268	1
		2011085H1	344	545	
		1831290H1	10	257	T^{T}
		3473958HI	70	242	
į		1972268F6	163	617	
157	1831290	1301277F1	413	852	
		1521574F1	1024	1602	
		1561690T6	1729	1058	
		891461R1	1261	1738	

TABLE 6 (cont.)

Nucleotide	Clone ID	L		
SEO ID NO.			Starting Nucleotide of	Ending Nucleotide of
		SEQ ID NO	Fragment	Fragment
		1831477HI	59	337
		1582867H1	_	661
		1336769T1	9861	0691
		1933092H1	525	789
158	1831477	1519909F1	841	1296
		1220946H1	1901	300
		809556T1	1983	1687
		1217559TI	2002	1445
		1309225F1	1747	2001
159	1841607	1841607HI	13	261
		SBHA03588F1	13	172
		1852391HI	86	798
091	1852391	734140H1	-	225
		1852391F6	86	542
		1854555H1		365
		2511711HI	37	58
191	1854555	782453R1	223	712
		1854555F6	_	346
		1840675T6	1046	860
		2109736H1	938	1054
		1855755HI	17	224
		3040236H1	_	179
162	1855755	1283207F1	306	816
		833763TI	1148	835
		1920926R6	854	1161
\$		1861434H1	13	253
50	1861434	1861434T6	872	261
		SARA01525FI	426	808
		SARA02548F1	587	889

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Nuclootide of
SEQ ID NO:		SEQ ID NO	Fragment	Fragment
		1872334H1	_	229
164	1872334	1872334F6	-	424
		SBGA03684F1	358	425
		1877230H1	1405	1677
		2519841H1	_	251
		1877230T6	1903	1405
,		1254693F1	335	716
165	1877230	077020R1	682	1414
		1232336F1	906	1507
		1004952R6	1451	1904
		SARA01879F1	1545	1921
		SARA02654F1	1545	1923
		1877885H1	89	323
991	1877885	508020F1	499	51
		2751126R6	219	516
		SARA02571F1	407	499
	-	1889269HI	757	1020
	-	1915551H1	_	191
ţ		629493X12	481	865
/91	1889269	1441289F1	693	865
		1215274X34F1	9011	1631
		1818447F6	1307	1540
		1208463R1	1372	1493
		1890243H1	6	268
•		SARA01884F1	521	168
891	1890243	SATA00046F1	1057	851
		SARA03294F1	1329	910
		SARA02790F1	1138	1535

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Nucleotide of
SEQ ID NO:		SEQ ID NO	Fragment	Fragment
		1900433H1		242
691	1900433	SATA00396F1	409	124
		SATA02742FI	_	294
		1909441HI	786	1048
		1398811F1	_	550
		3039939H1	607	876
170	1909441	3324740H1	685	944
		1442131F6	787	1232
		2254056H1	1423	1522
		2199453T6	1955	1351
		1698531H1	1968	1796
		1932226H1	294	510
		2320569H1	-	266
		1932226F6	294	685
171	1932226	2469455T6	1475	101
		2469455F6	1034	1492
		1907140F6	1158	1482
		SATA02592F1	857	518
		1932647H1	17	246
		1492745T1	1582	1418
172	1932647	1492745H1	1418	6651
		SASA02355F1	386	19
		SASA00117F1	250	695
	-	SASA00192F1	515	816
		2124245HI	45	061
		1235393F1	495	895
173	2124245	1402264F6	323	925
		1303990F1	682	1240
		1402264T6	1613	950

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Nucleotide of
SEQ ID NO:		SEQ ID NO	Fragment	Fragment
		2132626HI	406	651
		1723432T6	1299	746
174	2132626	2132626R6	406	904
		1736723T6	1292	857
		1504738F1	898	1320
175	2280639	2280639H1	28	303
		1377560F6	261	777
		2292356H1	717	896
		4086827H1	-	275
176	2292356	1754442F6	232	577
		3571126H1	497	808
		1601305F6	808	1464
177	2349310	2349310H1		236
		2349310T6	682	2
		2373227H1	298	524
		331644HI	801	1053
178	2373227	302685R6	1141	1496
		SASA02181F1	577	_
		SASA01923F1	963	466
		SASA03516F1	1102	1249
179	2457682	2457682H1		226
		2457682F6	-	554
081	2480426	2480426H1	-	213
		2480426F6	1	501

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Nucleotide of
SEQ ID NO:		SEQ ID NO	Fragment	Fragment
		2503743HI	9	222
		1853909HI	-	272
		1517619F1	172	830
181	2503743	1467896F6	540	1112
		490031F1	1647	1068
		1208654R1	1382	1633
		880544R1	1450	1648
		2537684HI	434	682
		2005493H1	_	194
		730969H1	307	547
182	2537684	916487H1	723	686
	`	996135R1	664	1598
		1920738R6	1306	1692
		1957710F6	1472	1692
		2593853HI		252
183	2593853	807497H1	2	217
		914020R6	284	740
		889992R1	416	729
		2622354HI	3	266
184	2622354	2623992H1	-	246
		1556510F6	81	258
		2641377H1	126	369
185	2641377	4341415H2	01	345
		SBCA07049F3	126	865

TABLE 6 (cont.)

Fragment 139 1486 1285 1423 819 973 20 1 291 63 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Nucleotide of
5 2674857H1 139 6 2674857 172857H1 1486 1 1728547H1 1285 301365F1 819 819 SBCA00694F1 973 20 2758485H1 20 2758485H1 1 2758485H1 20 2758485 309733H1 1 1 2763296H1 63 2 2763296H1 63 1 2763296H1 63 1 2763296H1 63 1 2763296H1 63 63 276326H1 1 1 2779436H1 1 2 2808528H1 25 2 2808528H1 25 2 2808528H1 25 2 2808528H1 1 1 2808528H1 2213849H1 1 280853R1 3036 6 2816821H1 1 6 2816821H1 1 1 2816821H1	SEQ ID NO:		SEQ ID NO	Fragment	Fragment
5 2674857 1872373H1 1 5 2674857 1728547H1 1285 3013651F6 1423 1423 3013651F6 1423 1423 3013651F6 1423 1423 3013651F6 1423 1423 3013651F6 11 20 2758485 3097533H1 1 2763296H1 63 291 2763296H1 63 1 2763296H1 63 1 2763296H1 63 63 2779436H1 1 1 2779436H1 1 25 2808528H1 25 2 2808528H1 2611513F6 2 2809230H1 409 6 2809230H1 1 409 2816821H1 1 1 2816821H1 1 1 2816821H6 1 1 2816821H6 1 1 2816821F6 210 28			2674857HI	139	393
5 2674857 470512R6 1486 5 3013651F6 1423 3013651F6 1423 3013651F6 1423 SBCA01366F1 819 SBCA01366F1 819 SBCA01366F1 819 SBCA01366F1 973 2758485H1 20 2762296H1 63 2763296H1 63 2763296H1 63 SBDA07002F3 63 2779436H1 1 2779436H1 1 2808528H1 25 2808528H1 25 2808528H1 25 2809530H1 409 2211349H1 1 2809230 711706R6 95832R1 2816821H1 1 2816821H1 1 2816821H1 1 2816821F6 959 959 959			1872373H1	_	270
5 2674857 1728547HI 1285 3013651F6 1423 1423 3013651F6 1423 1423 SBCA00694FI 819 1 2758485HI 20 2 2763296HI 63 2 1578959F6 291 1 2763296HI 63 1 2763296HI 63 1 SBDA07002F3 63 1 2779436HI 1 1 2779436HI 1 2 2808528HI 25 2 2808528HI 25 2 2808528HI 25 2 2808528HI 25 2 2808538HI 1 1 2809230HI 409 6 958323RI 407 6 281682HI 1 1 281682HI 1 1 281682H 281682HI 1 281682HI 2810 259 281682HI <t< td=""><td></td><td></td><td>470512R6</td><td>1486</td><td>1502</td></t<>			470512R6	1486	1502
SBCA0136F1 819	981	2674857	1728547111	1285	1508
SBCA01366F1 819 SBCA00694F1 973 SBCA00694F1 973 2758485H1 20 2758485H1 20 1578959F6 291 2763296H1 63 2763296H1 63 2763296H1 63 2763296H1 63 2763296H1 63 2763296H1 1 2763296H1 63 2779436H1 1 2779436H1 1 2779436H1 27 28DA07009F3 1 28BDA07021T3 1058 28BDA07021T3 1058 2213849H1 1 2809230H1 409 221849H1 1 2816821H1 210 2816821H1 210 2816821H1 1 2816821H1 1 2816821H2 1 2816821H2 210 2816821H2 210 2816821H2 259			3013651F6	1423	1987
SBCA00694F1 973 SBCA00694F1 20 2758485H1 20 1 1 1 1 1 1 1 1 1			SBCA01366F1	819	385
2758485 2758485H1 20 2758485 3097533H1 1 1578959F6 291 2763296H1 63 2763296H1 63 2779436H1 1 2779436H1 1 2779436F6 1 2779436F6 1 2808528H1 2 2808528H1 25 2808528H1 25 2808528H1 25 2809530H1 409 2213849H1 1 2809230H1 409 2213849H1 1 2816821H1 2213849H1 2213849H1 1 2213849H1 1 2213849H1 1 2213849H1 1 2213849H1 1 2816821H1 210 2816821H1 2816821H1 2816821H1 1 2816821H2 1 2816821H2 1 2816821H2 1 2816821H2 2816			SBCA00694F1	973	8611
2758485 3097533H1 1 1578959F6 291 2763296 3486025F6 1 2779436 3486025F6 1 2779436H1 1 1 2779436F6 1 1 2779436F6 1 2 2808528H1 25 2 2808528H1 25 2 2808528H1 25 2 2808528H1 25 2 2809230H1 409 6 2809230H1 409 6 958323R1 407 8 959 2210 2 2816821H1 210 2 2816821H1 1 1 2816821F6 210 6 2816821F6 2210 6 94872276 959 6			2758485H1	20	267
1578959F6 291 1578959F6 291 1578296H1 63 1486025F6 1 1 1 1 1 1 1 1 1	187	2758485	3097533H1	arma	158
2763296 2763296H1 63 3486025F6 1 SBDA07002F3 63 2779436H1 1 2779436H2 1 2779436F6 1 2808528H1 25 2808528H1 25 2808528H1 25 2809530H1 409 2213849H1 1 2216821H1 2816821H1 2816821H1 2816821H1 2816821H2 2816821H2 2816821F6 210 2816821F6 250 2816821F6 250 2816821F6 210 2816821F6 210 2816821F6 250 2816821F6 210 2			1578959F6	291	171
2763296 3486025F6 1 SBDA07002F3 63 2779436H1 1 2779436F6 1 SBDA07009F3 1 2808528H1 25 2808528H1 25 2808528H1 25 2809530H1 409 2213849H1 1 2809230 711706R6 396 95823R1 407 030732F1 1366 2816821H1 210 2816821H1 210 2816821F6 210 2816821F6 210 948722T6 959			2763296HI	63	301
SBDA07002F3 63 2779436H1 1 2779436H1 1 2808528H1 25 2808528H1 25 2808528H1 25 2809530H1 409 2213849H1 1 2809230 711706R6 396 95823R1 407 030732F1 1366 2816821H1 210 2816821F6 210	188	2763296	3486025F6	-	130
2779436 1 2779436F6 1 SBDA07009F3 1 2808528H1 25 2808528H1 25 2809528H1 25 2809230H1 409 2213849H1 1 2809230 711706R6 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 210 2816821F6 210 948722T6 959			SBDA07002F3	63	289
2779436 1 SBDA07009F3 1 2808528H1 25 2808528H1 25 2809230H1 409 2213849H1 1 2809230 711706R6 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 210 948722T6 959			2779436HI		233
SBDA07009F3 1 2808528H1 25 2808528H1 2 2808528H1 2 2809230H1 409 2213849H1 1 2809230 711706R6 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 210 948722T6 959	189	2779436	2779436F6	<u>·</u>	577
2808528 2808528H1 25 2808528 2611513F6 2 2809230H1 409 2213849H1 1 2213849H1 1 2809230 711706R6 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 210 948722T6 959			SBDA07009F3	_	809
2808528 2611513F6 2 SBDA07021T3 1058 2809230H1 409 2213849H1 1 2809230 711706R6 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 210 948722T6 959			2808528HI	25	335
SBDA07021T3 1058 2809230H1 409 2213849H1 1 2809230 711706R6 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 1 2816821F6 210 948722T6 959	061	2808528	2611513F6	2	489
2809230H1 409 2213849H1 1 2213849H1 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 210 948722T6 959			SBDA07021T3	1058	443
2213849H1 1 2809230 711706R6 396 958323R1 407 030732F1 1366 2816821H1 210 2816821F6 210 948722T6 959			2809230HI	409	630
2809230 711706R6 396 958323R1 407 030732F1 1366 2816821 3746964H1 1 2816821F6 210 948722T6 959			2213849HI	_	133
2816821 3746964H1 1 210 2816821 2816821F6 210 2816821F6 210 948722T6 959	161	2809230	711706R6	396	169
2816821 2816821H1 210 2816821 3746964H1 1 2 2816821F6 210 948722T6 959			958323R1	407	800
2816821 2816821H1 210 2816821F6 1 2816821F6 210 948722T6 959			030732F1	1366	623
2816821 3746964H1 1 2816821F6 210 948722T6 959	Ġ		2816821HI	210	501
210	192	2816821	3746964HI		307
959			2816821F6	210	682
			948722T6	959	527

TABLE 6 (cont.)

Nucleotide	Clone ID	Fragment of	Starting Nucleotide of	Ending Nucleotide of
SEQ ID NO:		SEQ ID NO	Fragment	Fragment
		2817268H1	42	282
		3591308H1	13	264
193	2817268	419522R1	179	808
		2073028F6	446	924
		1308781F6	698	1112
		2923165HI	8	295
		2011630H1	81	238
194	2923165	1457250F1	268	856
		754668R1	327	878
		1406510F6	558	106
195	2949822	2949822HI		280
		SBDA07078F3	-	909
		2992192HI	25	321
		2534324H2	-	240
961	2992192	2815255T6	069	219
		1551107T6	893	471
		1551107R6	471	069
		2992458HI	48	362
	•	2618951HI		247
		1479252F1	163	610
161	2992458	1879054H1	563	840
		1879054F6	563	9601
		2215240H1	951	1202
		1535968TI	1729	1173

TABLE 6 (cont.)

		-					_		_	_	
Ending Nucleotide of Fragment	952	192	268	1392	1487	1934	1544	2017	363	141	. 526
Starting Nucleotide of Fragment	652	94	06	830	1033	1432	2006	1894	72	523	380
Fragment of SEQ ID NO	3044710H1 3741773H1	859906X42C1	1534347F1	1421122F1	1303865F1	1704452F6	1251642F1	1781694R6	3120415H1	1360123T1	1375015H1
Clone ID				3044710						3120415	
Nucleotide SEQ ID NO:				198						199	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ 5 ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEO ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ 10 ID NO:31, SEQ ID NO:32, SEQ ID NO:33, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, 15 SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, SEQ ID NO:65, SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:77, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:80, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID 20 NO:84, SEQ ID NO:85, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, SEQ ID NO:90, SEQ ID NO:91, SEQ ID NO:92, SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:99, SEQ ID NO:100, SEQ ID NO:101, SEQ ID NO:102, SEQ ID NO:103, SEQ ID NO:104, SEQ ID NO:105, SEQ ID NO:106, SEQ ID NO:107, SEQ ID NO:108, SEQ ID NO:109, SEQ ID 25 NO:110, SEQ ID NO:111, SEQ ID NO:112, SEQ ID NO:113, SEQ ID NO:114, SEQ ID NO:115, SEQ ID NO:116, SEQ ID NO:117, SEQ ID NO:118, SEQ ID NO:119, SEQ ID NO:120, SEQ ID NO:121, SEQ ID NO:122, SEQ ID NO:123, SEQ ID NO:124, SEQ ID NO:125, SEQ ID NO:126, SEQ ID NO:127, SEQ ID NO:128, SEQ ID NO:129, SEQ ID NO:130, SEQ ID NO:131, SEQ ID NO:132, SEQ ID NO:133, SEQ ID NO:134 (SEQ ID 30 NO:1-134), and fragments thereof.

2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.

3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.

4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.

5

- 5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.
- 6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
- 7. A method for detecting a polynucleotide, the method comprising the steps 10 of:
 - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
 - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
 - 8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
- 9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:135, SEQ ID NO:136, SEQ 20 ID NO:137, SEQ ID NO:138, SEQ ID NO:139, SEQ ID NO:140, SEQ ID NO:141, SEQ ID NO:142, SEQ ID NO:143, SEQ ID NO:144, SEQ ID NO:145, SEQ ID NO:146, SEQ ID NO:147, SEQ ID NO:148, SEQ ID NO:149, SEQ ID NO:150, SEQ ID NO:151, SEQ ID NO:152, SEQ ID NO:153, SEQ ID NO:154, SEQ ID NO:155, SEQ ID NO:156, SEQ ID NO:157, SEQ ID NO:158, SEQ ID NO:159, SEQ ID NO:160, SEO ID NO:161, SEO 25 ID NO:162, SEQ ID NO:163, SEQ ID NO:164, SEQ ID NO:165, SEQ ID NO:166, SEQ ID NO:167, SEQ ID NO:168, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186, SEQ 30 ID NO:187, SEQ ID NO:188, SEQ ID NO:189, SEQ ID NO:190, SEQ ID NO:191, SEQ ID NO:192, SEQ ID NO:193, SEQ ID NO:194, SEQ ID NO:195, SEQ ID NO:196, SEQ ID NO:197, SEQ ID NO:198, SEQ ID NO:199, SEQ ID NO:200, SEQ ID NO:201, SEQ

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- 15 10. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 9.
 - 11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.
- 12. An expression vector comprising at least a fragment of the polynucleotide 20 of claim 3.
 - 13. A host cell comprising the expression vector of claim 12.
 - 14. A method for producing a polypeptide, the method comprising the steps of:
 - a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and
 - b) recovering the polypeptide from the host cell culture.
 - 15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.
 - 16. A purified antibody which specifically binds to the polypeptide of claim 1.
 - 17. A purified agonist of the polypeptide of claim 1.
- 30 18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of HSPP, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

A method for treating or preventing a disorder associated with increased
 expression or activity of HSPP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

SEQUENCE LISTING

```
<110> INCYTE PHARMACEUTICALS, INC.
      LAL, Preeti
      TANG, Y. Tom
      GORGONE, Gina A.
      CORLEY, Neil C.
      GUEGLER, Karl J.
      BAUGHN, Mariah R.
      AKERBLOM, Ingrid E.
      AU-YOUNG, Janice
      YUE, Henry
      PATTERSON, Chandra
      REDDY, Roopa
      HILLMAN, Jennifer L.
      BANDMAN, Olga
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Gly Ser Leu Leu Arg Gly Pro Arg Pro Arg Ile Pro Val Leu Val
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Ser Cys Gln Pro Val Lys Gly His Gly Thr Leu Gly Glu Ser Pro
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                                     40
Ile Val Phe Gly Gly Gln Lys Lys Ala Thr Phe Arg Tyr His Phe
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Phe His Gly Gln Ser Phe Tyr Ser Thr Arg Pro Pro Ser Ile His
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                                     85
Lys Asp Tyr Val Asn Arg Leu Phe Leu Asn Trp Thr Glu Gly Gln
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Glu Ser Gly Phe Leu Arg Ile Ser Asn Leu Arg Lys Glu Asp Gln
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Ser Trp His Leu Ser Leu Asp Thr Ala Ile Arg Val Ala Leu Ala
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Val Ala Val Leu Lys Thr Val Ile Leu Gly Leu Leu Cys Leu Leu
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Pro Lys His Val Tyr Ser Ile Ala Ser Lys Gly Ser Lys Phe Lys
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7/167

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Asp Gly Gly Gln Ala Glu Gly Ala Glu Asp Glu Leu Glu Val Arg
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Phe Asn Ala Pro Phe Asp Val Gly Ile Lys Leu Ser Gly Val Gln
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95

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Tyr Ser Pro Pro Glu Arg Thr Glu Ser Phe Asp Val Val Thr Lys
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Asp Pro Gly Asn His Asn Ser Gly Ile Asp Leu Leu Arg Thr Tyr
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Ser Leu Tyr Pro Thr Ile Ala Thr Gly Ile Leu His Leu Leu Ala
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Gly Leu Cys Thr Leu Gly Ser Val Ser Cys Tyr Val Ala Gly Ile
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Glu Leu Leu His Gln Lys Leu Glu Leu Pro Asp Asn Val Ser Gly
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Glu Phe Gly Trp Ser Phe Cys Leu Ala Cys Val Ser Ala Pro Leu
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Pro Thr Leu Pro Thr Pro Glu Arg Leu Pro Glu Gln Met Leu Phe
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Pro Ser Ser Ser Lys Pro Phe Ser Leu Leu Ser Leu Thr Ile
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Trp Ala Arg Leu Val Gly Arg Leu Thr Asn Arg Ile Cys Pro Val
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Pro Pro Gly Ser Val Ala Ser Ser Met Ser Leu Gln Ala Gly Arg
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<220>
<221> misc feature
<223> Incyte Clone No: 1603403
<400> 16
Met Gly Ser Gly Leu Pro Leu Val Leu Leu Leu Thr Leu Leu Gly
                                    10
Ser Ser His Gly Thr Gly Pro Gly Met Thr Leu Gln Leu Lys Leu
                20
                                    25
Lys Glu Ser Phe Leu Thr Asn Ser Ser Tyr Glu Ser Ser Phe Leu
                35
                                     40
Glu Leu Leu Glu Lys Leu Cys Leu Leu Leu His Leu Pro Ser Gly
                 50
                                     55
Thr Ser Val Thr Leu His His Ala Arg Ser Gln His His Val Val
                65
Cys Asn Thr
```

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<210> 17
<211> 71
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 1652303
<400> 17
Met Lys Leu Leu Ser Cys Leu Leu Phe Leu Lys Ala Pro Leu Tyr
                                     10
Pro Thr Leu Cys Ser Lys Asp Pro Arg Ala Gly His Ser Leu Ile
                 20
                                     25
Cys Gly Gln Ala Gly Gln Ile Pro Glu Ala Gln Leu Gly Phe Ser
                                     40
Ser Asp Phe Lys Leu Cys Trp Cys Trp Asp Gln Gln Lys Ala Asn
                 50
                                     55
Val Gln Pro Thr His Arg Thr Val Arg Gly Leu
<210> 18
<211> 188
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 1693358
Met Val Pro Gly Ala Ala Gly Trp Cys Cys Leu Val Leu Trp Leu
                                     10
Pro Ala Cys Val Ala Ala His Gly Phe Arg Ile His Asp Tyr Leu
                 20
                                     25
Tyr Phe Gln Val Leu Ser Pro Gly Asp Ile Arg Tyr Ile Phe Thr
                 35
                                    40
Ala Thr Pro Ala Lys Asp Phe Gly Gly Ile Phe His Thr Arg Tyr
                 50
                                     55
Glu Gln Ile His Leu Val Pro Ala Glu Pro Pro Glu Ala Cys Gly
                 65
                                     70
Glu Leu Ser Asn Gly Phe Phe Ile Gln Asp Gln Ile Ala Leu Val
                 80
                                     85
Glu Arg Gly Gly Cys Ser Phe Leu Ser Lys Thr Arg Val Val Gln
                 95
                                    100
Glu His Gly Gly Arg Ala Val Ile Ile Ser Asp Asn Ala Val Asp
                110
                                    115
Asn Asp Ser Phe Tyr Val Glu Met Ile Gln Asp Ser Thr Gln Arg
                125
                                    130
```

145

150

Thr Ala Asp Ile Pro Ala Leu Phe Leu Leu Gly Arg Asp Gly Tyr

```
Met Ile Arg Arg Ser Leu Glu Gln His Gly Leu Pro Trp Ala Ile
155 160 160 165

Ile Ser Ile Pro Val Asn Val Thr Ser Ile Pro Thr Phe Glu Leu
170 175 180

Leu Gln Pro Pro Trp Thr Phe Trp
185
```

<212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1707711 <400> 19 Met Lys Ala Gln Pro Leu Glu Ala Leu Leu Leu Val Ala Leu Val 5 10 Leu Ser Phe Cys Gly Val Trp Phe Glu Asp Trp Leu Ser Lys Trp 20 25 Arg Phe Gln Cys Ile Phe Gln Leu Ala His Gln Pro Ala Leu Val 35 40 Asn Ile Gln Phe Arg Gly Thr Val Leu Gly Ser Glu Thr Phe Leu 50 55 Gly Ala Glu Glu Asn Ser Ala Asp Val Arg Ser Trp Gln Thr Leu

65 Ser Tyr Phe Glu Leu

<210> 20 <211> 80 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1738735

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80

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<210> 21
<211> 84
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1749147
<400> 21
Met Gln Arg Pro Phe Leu Ser Val Pro Cys Leu Leu Leu Pro
                                    10
Ala Arg Val Val Trp Gly Cys Trp Cys Phe Leu Pro Gly Glu Asp
                 20
                                    25
Gly Gly Gly Cys Pro Thr Pro Ser Ser Gly Arg Ile Lys Leu Leu
                 35
                                    40
Gln Gln Cys Leu Leu His Pro Ser Leu Arg Ser Ile Thr Val Ser
                 50
                                    55
Arg Arg Ser Ala Gln Leu Leu Cys Arg Leu Lys Leu Gln Asn His
                 65
                                    70
Ile Pro Lys Val Pro Gly Lys Asn Val
                80
```

<210> 22 <211> 171 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1817722

<400> 22

Met His Met Ile Leu Lys Val Leu Thr Thr Ala Leu Leu Leu Gln 10 Ala Ala Ser Ala Leu Ala Asn Tyr Ile His Phe Ser Ser Tyr Ser 20 25 Lys Asp Gly Ile Gly Val Pro Phe Met Gly Ser Leu Ala Glu Phe 35 40 Phe Asp Ile Ala Ser Gln Ile Gln Met Leu Tyr Leu Leu Ser 50 55 Leu Cys Met Gly Trp Thr Ile Val Arg Met Lys Lys Ser Gln Ser 65 70 Arg Pro Leu Gln Trp Asp Ser Thr Pro Ala Ser Thr Gly Ile Ala 80 85 Val Phe Ile Val Met Thr Gln Ser Val Leu Leu Trp Glu Gln 95 100 Phe Glu Asp Ile Ser His His Ser Tyr His Ser His His Asn Leu 110 115

<210> 23 <211> 243 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1831290 <400> 23 Met Ser Ser Gly Thr Glu Leu Leu Trp Pro Gly Ala Ala Leu Leu Val Leu Leu Gly Val Ala Ala Ser Leu Cys Val Arg Cys Ser Arg 20 Pro Gly Ala Lys Arg Ser Glu Lys Ile Tyr Gln Gln Arg Ser Leu 40 Arg Glu Asp Gln Gln Ser Phe Thr Gly Ser Arg Thr Tyr Ser Leu 50 55 Val Gly Gln Ala Trp Pro Gly Pro Leu Ala Asp Met Ala Pro Thr 65 70 Arg Lys Asp Lys Leu Leu Gln Phe Tyr Pro Ser Leu Glu Asp Pro 80 85 Ala Ser Ser Arg Tyr Gln Asn Phe Ser Lys Gly Ser Arg His Gly 95 100 Ser Glu Glu Ala Tyr Ile Asp Pro Ile Ala Met Glu Tyr Tyr Asn 110 115 Trp Gly Arg Phe Ser Lys Pro Pro Glu Asp Asp Asp Ala Asn Ser 125 130 Tyr Glu Asn Val Leu Ile Cys Lys Gln Lys Thr Thr Glu Thr Gly 140 145 Ala Gln Gln Glu Gly Ile Gly Gly Leu Cys Arg Gly Asp Leu Ser 155 160 Leu Ser Leu Ala Leu Lys Thr Gly Pro Thr Ser Gly Leu Cys Pro 170 175 Ser Ala Ser Pro Glu Glu Asp Glu Glu Ser Glu Asp Tyr Gln Asn 185 190 Ser Ala Ser Ile His Gln Trp Arg Glu Ser Arg Lys Val Met Gly 200 205 Gln Leu Gln Arg Glu Ala Ser Pro Gly Pro Val Gly Ser Pro Asp 215 220 Glu Glu Asp Gly Glu Pro Asp Tyr Val Asn Gly Glu Val Ala Ala 235 Thr Glu Ala

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<210> 24
 <211> 311
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc feature
 <223> Incyte Clone No: 1831477
 Met Gly Val Pro Thr Ala Pro Glu Ala Gly Ser Trp Arg Trp Gly
 Ser Leu Leu Phe Ala Leu Phe Leu Ala Ala Ser Leu Gly Pro Val
                 20
Ala Ala Phe Lys Val Ala Thr Pro Tyr Ser Leu Tyr Val Cys Pro
                 35
                                     40
Glu Gly Gln Asn Val Thr Leu Thr Cys Arg Leu Leu Gly Pro Val
                 50
                                     55
Asp Lys Gly His Asp Val Thr Phe Tyr Lys Thr Trp Tyr Arg Ser
                 65
                                     70
Ser Arg Gly Glu Val Gln Thr Cys Ser Glu Arg Arg Pro Ile Arg
                 80
                                     85
Asn Leu Thr Phe Gln Asp Leu His Leu His His Gly Gly His Gln
                 95
                                    100
Ala Ala Asn Thr Ser His Asp Leu Ala Gln Arg His Gly Leu Glu
                110
                                    115
Ser Ala Ser Asp His His Gly Asn Phe Ser Ile Thr Met Arg Asn
                125
                                    130
Leu Thr Leu Leu Asp Ser Gly Leu Tyr Cys Cys Leu Val Val Glu
                140
                                    145
Ile Arg His His Ser Glu His Arg Val His Gly Ala Met Glu
                155
                                    160
Leu Gln Val Gln Thr Gly Lys Asp Ala Pro Ser Asn Cys Val Val
                170
                                    175
Tyr Pro Ser Ser Ser Gln Glu Ser Glu Asn Ile Thr Ala Ala Ala
                185
                                    190
Leu Ala Thr Gly Ala Cys Ile Val Gly Ile Leu Cys Leu Pro Leu
                200
                                    205
Ile Leu Leu Val Tyr Lys Gln Arg Gln Ala Ala Ser Asn Arg
                215
                                    220
Arg Ala Gln Glu Leu Val Arg Met Asp Ser Asn Ile Gln Gly Ile
                230
                                    235
Glu Asn Pro Gly Phe Glu Ala Ser Pro Pro Ala Gln Gly Ile Pro
                245
                                   250
Glu Ala Lys Val Arg His Pro Leu Ser Tyr Val Ala Gln Arg Gln
                260
                                   265
Pro Ser Glu Ser Gly Arg His Leu Leu Ser Glu Pro Ser Thr Pro
                275
                                   280
Leu Ser Pro Pro Gly Pro Gly Asp Val Phe Phe Pro Ser Leu Asp
               290
                                    295
Pro Val Pro Asp Ser Pro Asn Phe Glu Val Ile
               305
```

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<210> 25
<211> 57
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1841607
<400> 25
Met Ala Ser Ser Cys Phe Ser Leu Ser Phe Pro Pro Leu Ser Leu
                 5
                                     10
Ala Gly Ser Leu Ala Leu Trp Gly His Cys Cys Val Arg Leu Gly
                 20
                                     25
Cys Ser Phe Trp Ser Val Ser Ala Met Ala Gln Arg Leu Pro Ser
                 35
                                     40
Gln Asn Thr Tyr Asn Pro Pro Leu Cys Trp Ala Trp
                 50
<210> 26
<211> 82
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1852391
<400> 26
Met Phe Ser Leu Phe Ser Cys Leu Leu Ala Cys Leu Leu Asp Leu
                                     10
Leu Leu Ser Arg Val Ala Asp Glu Ala Phe Tyr Lys Gln Pro Phe
                 20
                                     25
Ala Asp Val Ile Gly Tyr Val Tyr Val Ala Lys Leu Ile Pro Phe
                                     40
Ser Thr Ser Asp Ser Phe Tyr Phe Cys Leu Glu Leu Met Leu Leu
                 50
                                     55
Leu Cys His Gln Leu Leu Cys Phe Leu Asn Tyr Phe Lys Leu Ala
                 65
                                     70
Leu Trp Gly Leu Pro Lys Asn
<210> 27
<211> 115
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1854555
```

```
<400> 27
Met Ala Gly Thr Val Leu Gly Val Gly Ala Gly Val Phe Ile Leu
Ala Leu Leu Trp Val Ala Val Leu Leu Cys Val Leu Leu Ser
                                    25
Arg Ala Ser Gly Ala Ala Arg Phe Ser Val Ile Phe Leu Phe Phe
                                    40
Gly Ala Val Ile Ile Thr Ser Val Leu Leu Leu Phe Pro Arg Ala
                50
                                    55
Gly Glu Phe Pro Ala Pro Glu Val Glu Val Lys Ile Val Asp Asp
                65
                                    70
Phe Phe Ile Gly Arg Tyr Val Leu Leu Ala Phe Leu Ser Ala Ile
                 80
                                    85
Phe Leu Gly Gly Leu Phe Leu Val Leu Ile His Tyr Val Leu Glu
                95
                                   100
Pro Ile Tyr Ala Lys Pro Leu His Ser Tyr
                110
```

<210> 28 <211> 327 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1855755

Met Ala Glu Leu Pro Gly Pro Phe Leu Cys Gly Ala Leu Leu Gly 10 Phe Leu Cys Leu Ser Gly Leu Ala Val Glu Val Lys Val Pro Thr 20 25 Glu Pro Leu Ser Thr Pro Leu Gly Lys Thr Ala Glu Leu Thr Cys 35 40 Thr Tyr Ser Thr Ser Val Gly Asp Ser Phe Ala Leu Glu Trp Ser 50 55 Phe Val Gln Pro Gly Lys Pro Ile Ser Glu Ser His Pro Ile Leu 65 70 Tyr Phe Thr Asn Gly His Leu Tyr Pro Thr Gly Ser Lys Ser Lys 80 85 Arg Val Ser Leu Leu Gln Asn Pro Pro Thr Val Gly Val Ala Thr 95 100 Leu Lys Leu Thr Asp Val His Pro Ser Asp Thr Gly Thr Tyr Leu 110 115 Cys Gln Val Asn Asn Pro Pro Asp Phe Tyr Thr Asn Gly Leu Gly 125 130 Leu Ile Asn Leu Thr Val Leu Val Pro Pro Ser Asn Pro Leu Cys 140 145 Ser Gln Ser Gly Gln Thr Ser Val Gly Gly Ser Thr Ala Leu Arg 155 160 Cys Ser Ser Ser Glu Gly Ala Pro Lys Pro Val Tyr Asn Trp Val 170 175 Arg Leu Gly Thr Phe Pro Thr Pro Ser Pro Gly Ser Met Val Gln 185

```
Asp Glu Val Ser Gly Gln Leu Ile Leu Thr Asn Leu Ser Leu Thr
               200
                                  205
Ser Ser Gly Thr Tyr Arg Cys Val Ala Thr Asn Gln Met Gly Ser
                                   220
Ala Ser Cys Glu Leu Thr Leu Ser Val Thr Glu Pro Ser Gln Gly
                                   235
Arg Val Ala Gly Ala Leu Ile Gly Val Leu Leu Gly Val Leu Leu
               245
                                   250
Leu Ser Val Ala Ala Phe Cys Leu Val Arg Phe Gln Lys Glu Arg
               260
                                   265
Gly Lys Lys Pro Lys Glu Thr Tyr Gly Gly Ser Asp Leu Arg Glu
               275
                                   280
Asp Ala Ile Ala Pro Gly Ile Ser Glu His Thr Cys Met Arg Ala
               290
                                   295
Asp Ser Ser Lys Gly Phe Leu Glu Arg Pro Ser Ser Ala Ser Thr
               305
                                  · 310
Val Thr Thr Lys Ser Lys Leu Pro Met Val Val
               320
```

<210> 29 <211> 133 <212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 1861434

<400> 29

Met Arg Met Ser Leu Ala Gln Arg Val Leu Leu Thr Trp Leu Phe 10 Thr Leu Leu Phe Leu Ile Met Leu Val Leu Lys Leu Asp Glu Lys 20 25 Ala Pro Trp Asn Trp Phe Leu Ile Phe Ile Pro Val Trp Ile Phe 35 40 Asp Thr Ile Leu Leu Val Leu Leu Ile Val Lys Met Ala Gly Arg 50 55 Cys Lys Ser Gly Phe Asp Pro Arg His Gly Ser His Asn Ile Lys 65 70 Lys Lys Ala Trp Tyr Leu Ile Ala Met Leu Leu Lys Leu Ala Phe 80 85 Cys Leu Ala Leu Cys Ala Lys Leu Glu Gln Phe Thr Thr Met Asn 95 100 Leu Ser Tyr Val Phe Ile Pro Leu Trp Ala Leu Leu Ala Gly Ala 110 115 Leu Thr Glu Leu Gly Tyr Asn Val Phe Phe Val Arg Asp

<210> 30

<211> 129

<212> PRT

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<213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte Clone No: 1872334
Met Gly Leu Thr Leu Leu Leu Leu Leu Leu Gly Leu Glu Gly
                                     10
Gln Gly Ile Val Gly Ser Leu Pro Glu Val Leu Gln Ala Pro Val
                 20
                                     25
Gly Ser Ser Ile Leu Val Gln Cys His Tyr Arg Leu Gln Asp Val
                 35
                                      40
Lys Ala Gln Lys Val Trp Cys Arg Phe Leu Pro Glu Gly Cys Gln
                 50
                                      55
Pro Leu Val Ser Ser Ala Val Asp Arg Arg Ala Pro Ala Gly Arg
                 65
Arg Thr Phe Leu Thr Asp Leu Gly Gly Leu Leu Gln Val Glu
                 80
                                      85
Met Val Thr Leu Gln Glu Glu Asp Ala Gly Glu Tyr Gly Cys Met
                 95
                                    100
Val Asp Gly Ala Arg Gly Pro Gln Ile Leu His Arg Val Ser Leu
                110
                                    115
Asn Ile Leu Pro Pro Gly Glu Leu Ser
                125
<210> 31
<211> 472
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1877230
<400> 31
Met Lys Phe Leu Ile Phe Ala Phe Phe Gly Gly Val His Leu Leu
                                     10
Ser Leu Cys Ser Gly Lys Ala Ile Cys Lys Asn Gly Ile Ser Lys
                 20
Arg Thr Phe Glu Glu Ile Lys Glu Glu Ile Ala Ser Cys Gly Asp
                 35
                                     40
Val Ala Lys Ala Ile Ile Asn Leu Ala Val Tyr Gly Lys Ala Gln
                 50
                                     55
Asn Arg Ser Tyr Glu Arg Leu Ala Leu Leu Val Asp Thr Val Gly
                 65
                                     70
Pro Arg Leu Ser Gly Ser Lys Asn Leu Glu Lys Ala Ile Gln Ile
                 80
                                     85
Met Tyr Gln Asn Leu Gln Gln Asp Gly Leu Glu Lys Val His Leu
                 95
                                    100
Glu Pro Val Arg Ile Pro His Trp Glu Arg Gly Glu Glu Ser Ala
```

115

130

Val Met Leu Glu Pro Arg Ile His Lys Ile Ala Ile Leu Gly Leu

```
Gly Ser Ser Ile Gly Thr Pro Pro Glu Gly Ile Thr Ala Glu Val
                140
                                    145
Leu Val Val Thr Ser Phe Asp Glu Leu Gln Arg Arg Ala Ser Glu
                155
                                    160
Ala Arg Gly Lys Ile Val Val Tyr Asn Gln Pro Tyr Ile Asn Tyr
                170
                                    175
Ser Arg Thr Val Gln Tyr Arg Thr Gln Gly Ala Val Glu Ala Ala
                185
                                    190
Lys Val Gly Ala Leu Ala Ser Leu Ile Arg Ser Val Ala Ser Phe
                200
                                    205
Ser Ile Tyr Ser Pro His Thr Gly Ile Gln Glu Tyr Gln Asp Gly
                215
                                    220
Val Pro Lys Ile Pro Thr Ala Cys Ile Thr Val Glu Asp Ala Glu
                230
                                    235
Met Met Ser Arg Met Ala Ser His Gly Ile Lys Ile Val Ile Gln
                245
                                    250
Leu Lys Met Gly Ala Lys Thr Tyr Pro Asp Thr Asp Ser Phe Asn
                260
                                    265
Thr Val Ala Glu Ile Thr Gly Ser Lys Tyr Pro Glu Gln Val Val
                275
                                    280
Leu Val Ser Gly His Leu Asp Ser Trp Asp Val Gly Gln Gly Ala
                290
                                    295
Met Asp Asp Gly Gly Gly Ala Phe Ile Ser Trp Glu Ala Leu Ser
                305
                                    310
Leu Ile Lys Asp Leu Gly Leu Arg Pro Lys Arg Thr Leu Arg Leu
                320
                                    325
Val Leu Trp Thr Ala Glu Glu Gln Gly Gly Val Gly Ala Phe Gln
                335
                                    340
Tyr Tyr Gln Leu His Lys Val Asn Ile Ser Asn Tyr Ser Leu Val
                350
                                    355
Met Glu Ser Asp Ala Gly Thr Phe Leu Pro Thr Gly Leu Gln Phe
                365
                                    370
Thr Gly Ser Glu Lys Ala Arg Ala Ile Met Glu Glu Val Met Ser
                380
                                    385
Leu Leu Gln Pro Leu Asn Ile Thr Gln Val Leu Ser His Gly Glu
                395
                                    400
Gly Thr Asp Ile Asn Phe Trp Ile Gln Ala Gly Val Pro Gly Ala
                410
                                    415
Ser Leu Leu Asp Asp Leu Tyr Lys Tyr Phe Phe Phe His His Ser
                425
                                    430
His Gly Asp Thr Met Thr Val Met Asp Pro Lys Gln Met Asn Val
                440
                                    445
Ala Ala Ala Val Trp Ala Val Val Ser Tyr Val Val Ala Asp Met
               455
Glu Glu Met Leu Pro Arg Ser
               470
```

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<210> 32
<211> 93
<212> PRT
<213> Homo sapiens
<220>
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<221> misc_feature

<223> Incyte Clone No: 1877885

<210> 33 <211> 92 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1889269

<400> 33 Met Asn Arg Pro Ser Ala Arg Asn Ala Leu Gly Asn Val Phe Val 10 Ser Glu Leu Leu Glu Thr Leu Ala Gln Leu Arg Glu Asp Arg Gln 20 Val Arg Val Leu Leu Phe Arg Ser Gly Val Lys Gly Val Phe Cys 35 40 Ala Gly Ala Asp Leu Lys Glu Arg Glu Gln Met Ser Glu Ala Glu 50 55 Val Gly Val Phe Val Gln Arg Leu Arg Gly Leu Met Asn Asp Ile 65 70 Gly Glu Asp Leu Gly Val Gly Trp Arg Arg Gly Phe Gly Gly Pro 80 Cys Arg

<210> 34 <211> 143 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1890243 <400> 34

Met Trp Ile Lys Gly Thr Met Lys Met Arg Gly Gly Lys Thr Ser Arg Ser Ala Val Leu Pro Val Ala Gln Leu Thr Leu Ile Ala Ser 25 Cys Phe Pro Asn Ser Gln Thr Val Leu Gly Thr Glu Gly Thr Leu 35 40 Asp Val Glu Ser Ser Pro Leu Ala Leu Leu Thr Gly Leu Trp Ala 50 55 Ser Pro Glu Ser Leu Ser Leu Tyr Leu Val Thr Leu Leu Cys Val 65 70 Cys Pro Ala Leu Gln Ser Cys Gln Gly Gln Gln Ala Asp Val Thr 80 85 Leu Ala Pro Cys Glu Ile Phe Ile Pro Gln Thr Leu Ala Cys Glu 95 100 Pro Phe Pro Ser Gln Trp Arg Ala Leu Lys Gly Ala Ser Leu Glu 110 115 Ser Ser Ser Val Leu Trp Val Ala Pro Cys Arg Trp Pro Leu Thr 125 Leu Arg Cys Ser Arg Val His Leu 140

<210> 35 <211> 89 <212> PRT <213> Homo sapiens <220> <221> misc feature <223> Incyte Clone No: 1900433 <400> 35 Met Glu Arg Val Thr Leu Ala Leu Leu Leu Leu Ala Gly Leu Thr 5 10 Ala Leu Glu Ala Asn Asp Pro Phe Ala Asn Lys Asp Pro Phe 20 25 Tyr Tyr Asp Trp Lys Asn Leu Gln Leu Ser Gly Leu Ile Cys Gly 35 40 Gly Leu Leu Ala Ile Ala Gly Ile Ala Ala Val Leu Ser Gly Lys 50 Cys Lys Tyr Lys Ser Ser Gln Lys Gln His Ser Pro Val Pro Glu 65 70 Lys Ala Ile Pro Leu Ile Thr Pro Gly Ser Ala Thr Thr Cys

<210> 36 <211> 560 <212> PRT <213> Homo sapiens <220> <221> misc feature

<223> Incyte Clone No: 1909441

Met Ala Lys Lys Leu Thr Glu Met Ile Pro Leu Cys Asn His Pro Ala Ser Phe Val Lys Leu Phe Val Ala Leu Gly Pro Ile Ala Gly Pro Glu Glu Lys Lys Gln Leu Lys Ser Thr Met Leu Leu Met Ser Glu Asp Leu Thr Gly Glu Gln Ala Leu Ala Val Leu Gly Ala Met Gly Asp Met Glu Ser Arg Asn Ser Cys Leu Ile Lys Arg Val Thr Ser Val Leu His Lys His Leu Asp Gly Tyr Lys Pro Leu Glu Leu Leu Lys Ile Thr Gln Glu Leu Thr Phe Leu His Phe Gln Arg Lys Glu Phe Phe Ala Lys Leu Arg Glu Leu Leu Ser Tyr Leu Lys Asn Ser Phe Ile Pro Thr Glu Val Ser Val Leu Val Arg Ala Ile Ser Leu Leu Pro Ser Pro His Leu Asp Glu Val Gly Ile Ser Arg Ile Glu Ala Val Leu Pro Gln Cys Asp Leu Asn Asn Leu Ser Ser Phe Ala Thr Ser Val Leu Arg Trp Ile Gln His Asp His Met Tyr Leu Asp Asn Met Thr Ala Lys Gln Leu Lys Leu Leu Gln Lys Leu Asp His Tyr Gly Arg Gln Arg Leu Gln His Ser Asn Ser Leu Asp Leu Leu Arg Lys Glu Leu Lys Ser Leu Lys Gly Asn Thr Phe Pro Glu Ser Leu Leu Glu Glu Met Ile Ala Thr Leu Gln His Phe Met Asp Asp Ile Asn Tyr Ile Asn Val Gly Glu Ile Ala Ser Phe Ile Ser Ser Thr Asp Tyr Leu Ser Thr Leu Leu Leu Asp Arg Ile Ala Ser Val Ala Val Gln Gln Ile Glu Lys Ile His Pro Phe Thr Ile Pro Ala Ile Ile Arg Pro Phe Ser Val Leu Asn Tyr Asp Pro Pro Gln Arg Asp Glu Phe Leu Gly Thr Cys Val Gln His Leu Asn Ser Tyr Leu Gly Ile Leu Asp Pro Phe Ile Leu Val Phe Leu Gly Phe Ser Leu Ala Thr Leu Glu Tyr Phe Pro Glu Asp Leu Leu Lys Ala Ile Phe Asn Ile Lys Phe Leu Ala Arg Leu Asp Ser Gln Leu Glu Ile Leu Ser Pro Ser Arg Ser Ala Arg Val Gln Phe His Leu Met Glu Leu Asn Arg Ser Val Cys Leu Glu Cys Pro Glu Phe Gln Ile Pro Trp Phe His Asp Arg Phe Cys Gln Gln Tyr Asn Lys Gly

```
Ile Gly Gly Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu
                410
                                    415
Ala Glu Val Leu Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu
                425
                                    430
Thr Pro Tyr Tyr His Lys Val Asp Phe Glu Cys Ile Leu Asp Lys
                440
                                    445
Arg Lys Lys Pro Leu Pro Tyr Gly Ser His Asn Ile Ala Leu Gly
                455
                                    460
Gln Leu Pro Glu Met Pro Trp Glu Ser Asn Ile Glu Ile Val Gly
                470
                                    475
Ser Arg Leu Pro Pro Gly Ala Glu Arg Ile Ala Leu Glu Phe Leu
                485
                                    490
Asp Ser Lys Ala Leu Cys Arg Asn Ile Pro His Met Lys Gly Lys
                                    505
Ser Ala Met Lys Lys Arg His Leu Glu Ile Leu Gly Tyr Arg Val
                515
                                    520
Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met Ala Leu Ser Thr
                530
                                    535
Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile Phe Gly Glu
                545
                                    550
Val Lys Ser Cys Leu
                560
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<211> 197 <212> PRT <213> Homo sapiens <220> <221> misc feature <223> Incyte Clone No: 1932226 <400> 37 Met Gly Val Pro Leu Gly Leu Gly Ala Ala Trp Leu Leu Ala Trp Pro Gly Leu Ala Leu Pro Leu Val Ala Met Ala Ala Gly Gly Arg Trp Val Arg Gln Gln Gly Pro Arg Val Arg Arg Gly Ile Ser Arg Leu Trp Leu Arg Val Leu Leu Arg Leu Ser Pro Met Ala Phe Arg 55 Ala Leu Gln Gly Cys Gly Ala Val Gly Asp Arg Gly Leu Phe Ala 65 Leu Tyr Pro Lys Thr Asn Lys Asp Gly Phe Arg Ser Arg Leu Pro Val Pro Gly Pro Arg Arg Arg Asn Pro Arg Thr Thr Gln His Pro 95 Leu Ala Leu Leu Ala Arg Val Trp Val Leu Cys Lys Gly Trp Asn 115 Trp Arg Leu Ala Arg Ala Ser Gln Gly Leu Ala Ser His Leu Pro 130 Pro Trp Ala Ile His Thr Leu Ala Ser Trp Gly Leu Leu Arg Gly 145 Glu Arg Pro Thr Arg Ile Pro Arg Leu Leu Pro Arg Ser Gln Arg

<210> 37

160

```
Gln Leu Gly Pro Pro Ala Ser Arg Gln Pro Leu Pro Gly Thr Leu
                170
                                    175
Ala Gly Arg Arg Ser Arg Thr Arg Gln Ser Arg Ala Leu Pro Pro
                185
                                    190
Trp Arg
<210> 38
<211> 437
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 1932647
<400> 38
Met Ser Ala Val Leu Leu Leu Ala Leu Leu Gly Phe Ile Leu Pro
Leu Pro Gly Val Gln Ala Leu Leu Cys Gln Phe Gly Thr Val Gln
                 20
His Val Trp Lys Val Ser Asp Leu Pro Arg Gln Trp Thr Pro Lys
                 35
Asn Thr Ser Cys Asp Ser Gly Leu Gly Cys Gln Asp Thr Leu Met
                 50
                                     55
Leu Ile Glu Ser Gly Pro Gln Val Ser Leu Val Leu Ser Lys Gly
                 65
                                     70
Cys Thr Glu Ala Lys Asp Gln Glu Pro Arg Val Thr Glu His Arg
                 80
Met Gly Pro Gly Leu Ser Leu Ile Ser Tyr Thr Phe Val Cys Arg
                 95
                                    100
Gln Glu Asp Phe Cys Asn Asn Leu Val Asn Ser Leu Pro Leu Trp
                110
                                    115
Ala Pro Gln Pro Pro Ala Asp Pro Gly Ser Leu Arg Cys Pro Val
                125
                                    130
Cys Leu Ser Met Glu Gly Cys Leu Glu Gly Thr Thr Glu Glu Ile
                140
                                    145
Cys Pro Lys Gly Thr Thr His Cys Tyr Asp Gly Leu Leu Arg Leu
                155
                                    160
Arg Gly Gly Gle Phe Ser Asn Leu Arg Val Gln Gly Cys Met
                170
                                    175
Pro Gln Pro Gly Cys Asn Leu Leu Asn Gly Thr Gln Glu Ile Gly
                185
                                    190
Pro Val Gly Met Thr Glu Asn Cys Asn Arg Lys Asp Phe Leu Thr
                200
                                    205
Cys His Arg Gly Thr Thr Ile Met Thr His Gly Asn Leu Ala Gln
                215
                                    220
Glu Pro Thr Asp Trp Thr Thr Ser Asn Thr Glu Met Cys Glu Val
                230
                                    235
Gly Gln Val Cys Gln Glu Thr Leu Leu Leu Ile Asp Val Gly Leu
                                    250
Thr Ser Thr Leu Val Gly Thr Lys Gly Cys Ser Thr Val Gly Ala
                                    265
Gln Asn Ser Gln Lys Thr Thr Ile His Ser Ala Pro Pro Gly Val
```

```
275
                                    280
Leu Val Ala Ser Tyr Thr His Phe Cys Ser Ser Asp Leu Cys Asn
                290
                                    295
Ser Ala Ser Ser Ser Ser Val Leu Leu Asn Ser Leu Pro Pro Gln
                305
                                    310
Ala Ala Pro Val Pro Gly Asp Arg Gln Cys Pro Thr Cys Val Gln
                320
                                    325
Pro Leu Gly Thr Cys Ser Ser Gly Ser Pro Arg Met Thr Cys Pro
                335
                                    340
Arg Gly Ala Thr His Cys Tyr Asp Gly Tyr Ile His Leu Ser Gly
                350
                                    355
Gly Gly Leu Ser Thr Lys Met Ser Ile Gln Gly Cys Val Ala Gln
                365
                                    370
Pro Ser Ser Phe Leu Leu Asn His Thr Arg Gln Ile Gly Ile Phe
                380
                                    385
Ser Ala Arg Glu Lys Arg Asp Val Gln Pro Pro Ala Ser Gln His
                395
                                    400
Glu Gly Gly Gly Ala Glu Gly Leu Glu Ser Leu Thr Trp Gly Val
                                    415
Gly Leu Ala Leu Ala Pro Ala Leu Trp Trp Gly Val Val Cys Pro
                                    430
Ser Cys
```

<210> 39 <211> 330 <212> PRT <213> Homo sapiens

<221> misc_feature <223> Incyte Clone No: 2124245

<400> 39

Met Glu Gly Ala Pro Pro Gly Ser Leu Ala Leu Arg Leu Leu Leu 5 Phe Val Ala Leu Pro Ala Ser Gly Trp Leu Thr Thr Gly Ala Pro 20 Glu Pro Pro Pro Leu Ser Gly Ala Pro Gln Asp Gly Ile Arg Ile 35 Asn Val Thr Thr Leu Lys Asp Asp Gly Asp Ile Ser Lys Gln Gln 50 Val Val Leu Asn Ile Thr Tyr Glu Ser Gly Gln Val Tyr Val Asn 65 Asp Leu Pro Val Asn Ser Gly Val Thr Arg Ile Ser Cys Gln Thr 80 85 Leu Ile Val Lys Asn Glu Asn Leu Glu Asn Leu Glu Glu Lys Glu 95 100 Tyr Phe Gly Ile Val Ser Val Arg Ile Leu Val His Glu Trp Pro 110 115 Met Thr Ser Gly Ser Ser Leu Gln Leu Ile Val Ile Gln Glu Glu 125 Val Val Glu Ile Asp Gly Lys Gln Val Gln Gln Lys Asp Val Thr Glu Ile Asp Ile Leu Val Lys Asn Arg Gly Val Leu Arg His Ser

```
155
                                   160
                                                       165
Asn Tyr Thr Leu Pro Leu Glu Glu Ser Met Leu Tyr Ser Ile Ser
               170
                                   175
Arg Asp Ser Asp Ile Leu Phe Thr Leu Pro Asn Leu Ser Lys Lys
               185
                                   190
Glu Ser Val Ser Ser Leu Gln Thr Thr Ser Gln Tyr Leu Ile Arg
               200
                                   205
Asn Val Glu Thr Thr Val Asp Glu Asp Val Leu Pro Gly Lys Leu
               215
                                   220
Pro Glu Thr Pro Leu Arg Ala Glu Pro Pro Ser Ser Tyr Lys Val
               230
                                   235
Met Cys Gln Trp Met Glu Lys Phe Arg Lys Asp Leu Cys Arg Phe
               245
                                   250
Trp Ser Asn Val Phe Pro Val Phe Phe Gln Phe Leu Asn Ile Met
               260
                                   265
Val Val Gly Ile Thr Gly Ala Ala Val Val Ile Thr Ile Leu Lys
               275
                                   280
Val Phe Phe Pro Val Ser Glu Tyr Lys Gly Ile Leu Gln Leu Asp
               290
                                   295
Lys Val Asp Val Ile Pro Val Thr Ala Ile Asn Leu Tyr Pro Asp
               305
                                  310
Gly Pro Glu Lys Arg Ala Glu Asn Leu Glu Asp Lys Thr Cys Ile
                                   325
```

<211> 148 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 2132626 Met Glu Thr Gly Ala Leu Arg Arg Pro Gln Leu Leu Pro Leu Leu 5 . 10 Leu Leu Cys Gly Gly Cys Pro Arg Ala Gly Gly Cys Asn Glu 20 25 Thr Gly Met Leu Glu Arg Leu Pro Leu Cys Gly Lys Ala Phe Ala 35 40 Asp Met Met Gly Lys Val Asp Val Trp Lys Trp Cys Asn Leu Ser 50 55 Glu Phe Ile Val Tyr Tyr Glu Ser Phe Thr Asn Cys Thr Glu Met 65 70 Glu Ala Asn Val Val Gly Cys Tyr Trp Pro Asn Pro Leu Ala Gln 80 Gly Phe Ile Thr Gly Ile His Arg Gln Phe Phe Ser Asn Cys Thr 95 100 Val Asp Arg Val His Leu Glu Asp Pro Pro Asp Glu Val Leu Ile 110 115 Pro Leu Ile Val Ile Pro Val Val Leu Thr Val Ala Met Ala Gly 125 130 Leu Val Val Trp Arg Ser Lys Arg Thr Asp Thr Leu Leu

<210> 40

<210> 42

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<210> 41
<211> 188
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2280639
Met Ala Pro Pro Pro Pro Ser Pro Gln Leu Leu Leu Ala Ala
                 5
                                    10
Leu Ala Arg Leu Leu Gly Pro Ser Glu Val Met Ala Gly Pro Ala
                20
Glu Glu Ala Gly Ala His Cys Pro Glu Ser Leu Trp Pro Leu Pro
                35
                                    40
Pro Gln Val Ser Pro Arg Val Thr Tyr Thr Arg Val Ser Pro Gly
                50
                                    55
Gln Ala Glu Asp Val Thr Phe Leu Tyr His Pro Cys Ala His Pro
                65
                                    70
Trp Leu Lys Leu Gln Leu Ala Leu Leu Ala Tyr Ala Cys Met Ala
                80
                                    85
Asn Pro Ser Leu Thr Pro Asp Phe Ser Leu Thr Gln Asp Arg Pro
                95
                                   100
Leu Val Leu Thr Ala Trp Gly Leu Ala Leu Glu Met Ala Trp Val
               110
                                   115
Glu Pro Ala Trp Ala Ala His Trp Leu Met Arg Arg Arg Arg
               125
                                   130
Lys Gln Arg Lys Lys Ala Trp Ile Tyr Cys Glu Ser Leu Ser
               140
                                   145
Gly Pro Ala Pro Ser Glu Pro Thr Pro Gly Arg Gly Arg Leu Cys
               155
                                  160
Arg Arg Gly Cys Val Gln Ala Leu Ala Leu Ala Phe Ala Leu Arg
               170
                                  175
Thr Gly Gly Pro Leu Ala Gln Arg
               185
```

```
Pro Trp Lys Glu Ala Leu Val Arg Pro Pro Gly Ser Tyr Ser Ser
                 35
Ser Ser Asn Ser Gly Asp Trp Gly Trp Asp Leu Ala Ser Asp Gln
                 50
                                     55
Ser Ser Pro Ser Thr Pro Ser Pro Pro Leu Pro Pro Glu Ala Ala
                 65
                                     70
His Phe Leu Phe Gly Glu Pro Thr Leu Arg Lys Arg Lys Ser Pro
                 80
                                    85
Ala Gln Val Met Phe Gln Cys Leu Trp Lys Ser Cys Gly Lys Val
                95
                                   100
Leu Ser Thr Ala Ser Ala Met Gln Arg His Ile Arg Leu Val His
               110
                                   115
Leu Gly Cys Gly Gly Ala Trp Gly Ala Ala Gly Pro Ala Gly Trp
                125
                                   130
Leu Gly Leu Leu Gly Pro Ala Arg Pro Pro Leu Gln Leu Pro Leu
                140
                                   145
Ala Gly Cys Val Ser Arg Arg Gln Ala Glu Pro Glu Gln Ser
                155
                                   160
Asp Gly Glu Glu Asp Phe Tyr Tyr Thr Glu Leu Asp Val Gly Val
                170
                                   175
Asp Thr Leu Thr Asp Gly Leu Ser Ser Leu Thr Pro Val Phe Pro
                185
                                   190
Glu Gly Phe His Ala Ser Leu Pro Ser Pro Ala Leu Lys Leu Arg
                200
                                   205
Arg Leu Gly Gly Thr Arg Gln Pro Arg Gln Tyr Pro
               215
                                   220
```

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<210> 43
<211> 111
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2349310
<400> 43
Met Gly Pro Ser Ser Cys Leu Leu Leu Ile Leu Ile Pro Leu Leu
                                     10
Gln Leu Ile Asn Leu Gly Ser Thr Gln Cys Ser Leu Asp Ser Val
                 20
                                     25
Met Asp Lys Lys Ile Lys Asp Val Leu Asn Ser Leu Glu Tyr Ser
                 35
                                     40
Pro Ser Pro Ile Ser Lys Lys Leu Ser Cys Ala Ser Val Lys Ser
                 50
                                     55
Gln Gly Arg Pro Ser Ser Cys Pro Ala Gly Met Ala Val Thr Gly
                 65
                                     70
Cys Ala Cys Gly Tyr Gly Cys Gly Ser Trp Asp Val Gln Leu Glu
                 80
                                     85
Thr Thr Cys His Cys Gln Cys Ser Val Val Asp Trp Thr Thr Ala
                 95
                                    100
Arg Cys Cys His Leu Thr
                110
```

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<210> 44
  <211> 341
  <212> PRT
  <213> Homo sapiens
  <220>
  <221> misc_feature
  <223> Incyte Clone No: 2373227
 <400> 44
 Met Val Pro Ala Ala Gly Ala Leu Leu Trp Val Leu Leu Asn
                                      10
 Leu Gly Pro Arg Ala Ala Gly Ala Gln Gly Leu Thr Gln Thr Pro
                  20
                                     25
 Thr Glu Met Gln Arg Val Ser Leu Arg Phe Gly Gly Pro Met Thr
                  35
                                      40
 Arg Ser Tyr Arg Ser Thr Ala Arg Thr Gly Leu Pro Arg Lys Thr
                  50
                                      55
 Arg Ile Ile Leu Glu Asp Glu Asn Asp Ala Met Ala Asp Ala Asp
                  65
                                      70
 Arg Leu Ala Gly Pro Ala Ala Ala Glu Leu Leu Ala Ala Thr Val
                  80
                                      85
 Ser Thr Gly Phe Ser Arg Ser Ser Ala Ile Asn Glu Glu Asp Gly
                  95
                                     100
 Ser Ser Glu Glu Gly Val Val Ile Asn Ala Gly Lys Asp Ser Thr
                 110
                                     115
 Ser Arg Glu Leu Pro Ser Ala Thr Pro Asn Thr Ala Gly Ser Ser
                 125
                                     130
 Ser Thr Arg Phe Ile Ala Asn Ser Gln Glu Pro Glu Ile Arg Leu
                 140
                                     145
 Thr Ser Ser Leu Pro Arg Ser Pro Gly Arg Ser Thr Glu Asp Leu
                 155
                                     160
Pro Gly Ser Gln Ala Thr Leu Ser Gln Trp Ser Thr Pro Gly Ser
                 170
                                     175
Thr Pro Ser Arg Trp Pro Ser Pro Ser Pro Thr Ala Met Pro Ser
                                     190
Pro Glu Asp Leu Arg Leu Val Leu Met Pro Trp Gly Pro Trp His
                                     205
Cys His Cys Lys Ser Gly Thr Met Ser Arg Ser Arg Ser Gly Lys
                215
                                     220
Leu His Gly Leu Ser Gly Arg Leu Arg Val Gly Ala Leu Ser Gln
                                    235
Leu Arg Thr Glu His Lys Pro Cys Thr Tyr Gln Gln Cys Pro Cys
                                    250
Asn Arg Leu Arg Glu Glu Cys Pro Leu Asp Thr Ser Leu Cys Thr
                                    265
Asp Thr Asn Cys Ala Ser Gln Ser Thr Thr Ser Thr Arg Thr Thr
                275
                                    280
Thr Thr Pro Phe Pro Thr Ile His Leu Arg Ser Ser Pro Ser Leu
                290
                                    295
Pro Pro Ala Ser Pro Cys Pro Ala Leu Ala Phe Trp Lys Arg Val
                305
                                    310
Arg Ile Gly Leu Glu Asp Ile Trp Asn Ser Leu Ser Ser Val Phe
                320
                                    325
Thr Glu Met Gln Pro Ile Asp Arg Asn Gln Arg
```

335 340

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<210> 45
 <211> 148
 <212> PRT
 <213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2457682
<400> 45
Met Ala Gly Leu Ala Ala Arg Leu Val Leu Leu Ala Gly Ala Ala
 1
                  5
                                     10
Ala Leu Ala Ser Gly Ser Gln Gly Asp Arg Glu Pro Val Tyr Arg
                 20
                                     25
Asp Cys Val Leu Gln Cys Glu Glu Gln Asn Cys Ser Gly Gly Ala
                 35
                                      40
Leu Asn His Phe Arg Ser Arg Gln Pro Ile Tyr Met Ser Leu Ala
                 50
                                     55
Gly Trp Thr Cys Arg Asp Asp Cys Lys Tyr Glu Cys Met Trp Val
                 65
                                     70
Thr Val Gly Leu Tyr Leu Gln Glu Gly His Lys Val Pro Gln Phe
                 80
                                     85
His Gly Lys Trp Pro Phe Ser Arg Phe Leu Phe Phe Gln Glu Pro
                 95
                                    100
Ala Ser Ala Val Ala Ser Phe Leu Asn Gly Leu Ala Ser Leu Val
                110
                                    115
Met Leu Cys Arg Tyr Arg Thr Phe Val Pro Ala Ser Ser Pro Met
                125
                                    130
Tyr His Thr Cys Val Ala Phe Ala Trp Leu Ser Gly Arg
                140
                                    145
```

<210> 46
<211> 87
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2480426

<400> 46

Arg Ser Ala Phe Ser Ala Lys Arg Ser Glu Ile Arg Val Pro Pro
65 70 75

Leu Ser Asp Ala Pro Leu Pro Ser Thr Ala Cys Trp
80 85

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<210> 47
 <211> 383
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte Clone No: 2503743
 <400> 47
 Met Ala Gly Ile Pro Gly Leu Leu Phe Leu Leu Phe Phe Leu Leu
                                       10
 Cys Ala Val Gly Gln Val Ser Pro Tyr Ser Ala Pro Trp Lys Pro
                  20
                                      25
 Thr Trp Pro Ala Tyr Arg Leu Pro Val Val Leu Pro Gln Ser Thr
                  35
                                      40
 Leu Asn Leu Ala Lys Pro Asp Phe Gly Ala Glu Ala Lys Leu Glu
                  50
                                      55
 Val Ser Ser Cys Gly Pro Gln Cys His Lys Gly Thr Pro Leu
                  65
                                      70
 Pro Thr Tyr Glu Glu Ala Lys Gln Tyr Leu Ser Tyr Glu Thr Leu
                                      85
 Tyr Ala Asn Gly Ser Arg Thr Glu Thr Gln Val Gly Ile Tyr Ile
                                     100
Leu Ser Ser Ser Gly Asp Gly Ala Gln His Arg Asp Ser Gly Ser
                 110
                                     115
Ser Gly Lys Ser Arg Arg Lys Arg Gln Ile Tyr Gly Tyr Asp Ser
                                    130
                                                         135
Arg Phe Ser Ile Phe Gly Lys Asp Phe Leu Leu Asn Tyr Pro Phe
                140
                                     145
Ser Thr Ser Val Lys Leu Ser Thr Gly Cys Thr Gly Thr Leu Val
                155
                                     160
Ala Glu Lys His Val Leu Thr Ala Ala His Cys Ile His Asp Gly
                170
                                     175
Lys Thr Tyr Val Lys Gly Thr Gln Lys Leu Arg Val Gly Phe Leu
Lys Pro Lys Phe Lys Asp Gly Gly Arg Gly Ala Asn Asp Ser Thr
                200
Ser Ala Met Pro Glu Gln Met Lys Phe Gln Trp Ile Arg Val Lys
                215
Arg Thr His Val Pro Lys Gly Trp Ile Lys Gly Asn Ala Asn Asp
                230
                                                        240
Ile Gly Met Asp Tyr Asp Tyr Ala Leu Leu Glu Leu Lys Lys Pro
                245
His Lys Arg Lys Phe Met Lys Ile Gly Val Ser Pro Pro Ala Lys
                                                        270
Gln Leu Pro Gly Gly Arg Ile His Phe Ser Gly Tyr Asp Asn Asp
                275
                                    280
Arg Pro Gly Asn Leu Val Tyr Arg Phe Cys Asp Val Lys Asp Glu
```

```
290
                                    295
Thr Tyr Asp Leu Leu Tyr Gln Gln Cys Asp Ala Gln Pro Gly Ala
                305
                                    310
Ser Gly Ser Gly Val Tyr Val Arg Met Trp Lys Arg Gln Gln Gln
                320
                                    325
Lys Trp Glu Arg Lys Ile Ile Gly Ile Phe Ser Gly His Gln Trp
                335
                                    340
Val Asp Met Asn Gly Ser Pro Gln Asp Phe Asn Val Ala Val Arg
                350
                                    355
Ile Thr Pro Leu Lys Tyr Ala Gln Ile Cys Tyr Trp Ile Lys Gly
                365
                                    370
                                                        375
Asn Tyr Leu Asp Cys Arg Glu Gly
                380
```

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<211> 109
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2537684
<400> 48
Met Leu Leu Pro Ala Leu Cys Ala Trp Leu Leu Trp Val Pro Trp
                                     10
Cys Leu Leu Val Ala Gly Ser Gly Arg Ser Gly Gly Glu Leu Cys
                 20
                                     25
Cys Ser Ser Tyr Gly Val Ser Val Ile Ser Val Trp Ser Lys Cys
                 35
                                     40
Ser Val Cys Arg Cys Leu Met Gly Ser Val Pro Arg Ile Phe Phe
                 50
                                     55
Ala Phe Tyr Pro Ile Ala Trp Leu Pro Leu Pro Gly Ser Gln Gly
                 65
                                     70
Cys Trp Ser Arg Ser Trp Glu Trp Pro Leu Val Glu Pro Ala Ser
                 80
                                     85
Cys Leu Val Cys Leu Cys Phe Thr Phe Gly Val Leu Ser Gly Val
                 95
                                    100
Val Ala Val Lys
```

<210> 48

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<210> 49
<211> 185
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2593853
<400> 49
Met Lys Phe Thr Ile Val Phe Ala Gly Leu Leu Gly Val Phe Leu
```

```
10
Ala Pro Ala Leu Ala Asn Tyr Asn Ile Asn Val Asn Asp Asp Asn
                 20
                                     25
Asn Asn Ala Gly Ser Gly Gln Gln Ser Val Ser Val Asn Asn Glu
                 35
                                     40
His Asn Val Ala Asn Val Asp Asn Asn Gly Trp Asp Ser Trp
                 50
                                     55
Asn Ser Ile Trp Asp Tyr Gly Asn Gly Phe Ala Ala Thr Arg Leu
                 65
                                     70
Phe Gln Lys Lys Thr Cys Ile Val His Lys Met Asn Lys Glu Val
                 80
Met Pro Ser Ile Gln Ser Leu Asp Ala Leu Val Lys Glu Lys Lys
                 95
                                    100
Leu Gln Gly Lys Gly Pro Gly Gly Pro Pro Pro Lys Gly Leu Met
                110
                                    115
Tyr Ser Val Asn Pro Asn Lys Val Asp Asp Leu Ser Lys Phe Gly
                125
                                   130
Lys Asn Ile Ala Asn Met Cys Arg Gly Ile Pro Thr Tyr Met Ala
                140
                                    145
Glu Glu Met Gln Glu Ala Ser Leu Phe Phe Tyr Ser Gly Thr Cys
                155
                                   160
Tyr Thr Thr Ser Val Leu Trp Ile Val Asp Ile Ser Phe Cys Gly
                170
                                   175
Asp Thr Val Glu Asn
                185
```

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<210> 50
<211> 110
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2622354
Met Ala Pro Arg Gly Cys Ile Val Ala Val Phe Ala Ile Phe Cys
Ile Ser Arg Leu Leu Cys Ser His Gly Ala Pro Val Ala Pro Met
                 20
Thr Pro Tyr Leu Met Leu Cys Gln Pro His Lys Arg Cys Gly Asp
                 35
                                     40
Lys Phe Tyr Asp Pro Leu Gln His Cys Cys Tyr Asp Asp Ala Val
                 50
                                     55
Val Pro Leu Ala Arg Thr Gln Thr Cys Gly Asn Cys Thr Phe Arg
                 65
                                     70
Val Cys Phe Glu Gln Cys Cys Pro Trp Thr Phe Met Val Lys Leu
                 80
                                     85
Ile Asn Gln Asn Cys Asp Ser Ala Arg Thr Ser Asp Asp Arg Leu
                 95
                                    100
Cys Arg Ser Val Ser
                110
```

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<212> PRT
  <213> Homo sapiens
  <220>
  <221> misc_feature
  <223> Incyte Clone No: 2641377
  <400> 51
  Met Trp Leu Gly Ser Trp Leu Thr Ser Leu Leu Leu Ser Pro Tyr
                                       10
  Gly Ser Gly Trp Glu Lys Val Pro Cys Cys Val Thr Gly His Leu
                   20
 Arg Ser Cys Ser Cys Cys Leu Leu Gly Leu Ala Gly Val Gln Ser
                   35
                                       40
 Asp His Phe Ser Glu Gly Phe Phe Ser Glu Tyr Ser Ser Asp Val
                  50
                                       55
 Leu Pro Trp Gly Arg Arg Ser Phe Leu Pro Gln Gly Asp Ala Ser
                  65
                                      70
 Leu Leu Ala Cys Glu Cys Phe Leu His Leu Gln Val Val Trp Gly
                  80
                                      85
 Gln Phe Cys Leu Leu Glu Ala Trp Ala Gly Phe Thr Glu Gly Ser
                  95
                                     100
 Met Pro Ala Pro Ser Cys Arg Val His Phe Trp Cys Arg Val Asn
                 110
                                     115
 Thr Cys Ala Phe Met Ser
                 125
<210> 52
<211> 488
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2674857
<400> 52
Met Ala Gly Lys Gly Ser Ser Gly Arg Arg Pro Leu Leu Gly
Leu Leu Val Ala Val Ala Thr Val His Leu Val Ile Cys Pro Tyr
                                     10
                 20
                                     25
Thr Lys Val Glu Glu Ser Phe Asn Leu Gln Ala Thr His Asp Leu
                 35
                                     40
Leu Tyr His Trp Gln Asp Leu Glu Gln Tyr Asp His Leu Glu Phe
                 50
                                    55
Pro Gly Val Val Pro Arg Thr Phe Leu Gly Pro Val Val Ile Ala
                65
```

<210> 51 <211> 126

70

85

100

Val Phe Ser Ser Pro Ala Val Tyr Val Leu Ser Leu Leu Glu Met

Ser Lys Phe Tyr Ser Gln Leu Ile Val Arg Gly Val Leu Gly Leu

80

```
Gly Val Ile Phe Gly Leu Trp Thr Leu Gln Lys Glu Val Arg Arg
                                      115
 His Phe Gly Ala Met Val Ala Thr Met Phe Cys Trp Val Thr Ala
                 125
                                      130
 Met Gln Phe His Leu Met Phe Tyr Cys Thr Arg Thr Leu Pro Asn
                                     145
 Val Leu Ala Leu Pro Val Val Leu Leu Ala Leu Ala Ala Trp Leu
                 155
                                     160
 Arg His Glu Trp Ala Arg Phe Ile Trp Leu Ser Ala Phe Ala Ile
                 170
                                     175
 Ile Val Phe Arg Val Glu Leu Cys Leu Phe Leu Gly Leu Leu
                 185
                                     190
 Leu Leu Ala Leu Gly Asn Arg Lys Val Ser Val Val Arg Ala Leu
                 200
                                     205
 Arg His Ala Val Pro Ala Gly Ile Leu Cys Leu Gly Leu Thr Val
                 215
                                    220
 Ala Val Asp Ser Tyr Phe Trp Arg Gln Leu Thr Trp Pro Glu Gly
                 230
                                     235
 Lys Val Leu Trp Tyr Asn Thr Val Leu Asn Lys Ser Ser Asn Trp
                 245
                                     250
 Gly Thr Ser Pro Leu Leu Trp Tyr Phe Tyr Ser Ala Leu Pro Arg
                 260
                                     265
 Gly Leu Gly Cys Ser Leu Leu Phe Ile Pro Leu Gly Leu Val Asp
                275
                                     280
 Arg Arg Thr His Ala Pro Thr Val Leu Ala Leu Gly Phe Met Ala
                290
                                     295
Leu Tyr Ser Leu Leu Pro His Lys Glu Leu Arg Phe Ile Ile Tyr
                                     310
Ala Phe Pro Met Leu Asn Ile Thr Ala Ala Arg Gly Cys Ser Tyr
                                     325
Leu Leu Asn Asn Tyr Lys Lys Ser Trp Leu Tyr Lys Ala Gly Ser
                335
                                    340
Leu Leu Val Ile Gly His Leu Val Val Asn Ala Ala Tyr Ser Ala
                350
                                    355
Thr Ala Leu Tyr Val Ser His Phe Asn Tyr Pro Gly Gly Val Ala
                365
                                    370
Met Gln Arg Leu His Gln Leu Val Pro Pro Gln Thr Asp Val Leu
                                    385
Leu His Ile Asp Val Ala Ala Gln Thr Gly Val Ser Arg Phe
                395
                                    400
Leu Gln Val Asn Ser Ala Trp Arg Tyr Asp Lys Arg Glu Asp Val
                                    415
Gln Pro Gly Thr Gly Met Leu Ala Tyr Thr His Ile Leu Met Glu
                425
                                    430
Ala Ala Pro Gly Leu Leu Ala Leu Tyr Arg Asp Thr His Arg Val
                440
                                    445
Leu Ala Ser Val Val Gly Thr Thr Gly Val Ser Leu Asn Leu Thr
                455
                                    460
Gln Leu Pro Pro Phe Asn Val His Leu Gln Thr Lys Leu Val Leu
               470
                                   475
Leu Glu Arg Leu Pro Arg Pro Ser
               485
```

<210> 53

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<211> 197
 <212> PRT
 <213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2758485
<400> 53
Met Ser Pro Arg Arg Thr Leu Pro Arg Pro Leu Ser Leu Cys Leu
Ser Leu Cys Leu Cys Leu Cys Leu Ala Ala Leu Gly Ser Ala
                 20
Gln Ser Gly Ser Cys Arg Asp Lys Lys Asn Cys Lys Val Val Phe
                 35
                                     40
Ser Gln Gln Glu Leu Arg Lys Arg Leu Thr Pro Leu Gln Tyr His
                 50
                                     55
Val Thr Gln Glu Lys Gly Thr Glu Ser Ala Phe Glu Gly Glu Tyr
                 65
Thr His His Lys Asp Pro Gly Ile Tyr Lys Cys Val Val Cys Gly
                 80
                                     85
Thr Pro Leu Phe Lys Ser Glu Thr Lys Phe Asp Ser Gly Ser Gly
                 95
                                    100
Trp Pro Ser Phe His Asp Val Ile Asn Ser Glu Ala Ile Thr Phe
                110
                                    115
Thr Asp Asp Phe Ser Tyr Gly Met His Arg Val Glu Thr Ser Cys
                125
                                    130
Ser Gln Cys Gly Ala His Leu Gly His Ile Phe Asp Asp Gly Pro
                140
                                    145
Arg Pro Thr Gly Lys Arg Tyr Cys Ile Asn Ser Ala Ala Leu Ser
                155
                                    160
Phe Thr Pro Ala Asp Ser Ser Gly Thr Ala Glu Gly Gly Ser Gly
                                   175
Val Ala Ser Pro Ala Gln Ala Asp Lys Ala Asp Ser Glu Ser Asn
                185
                                   190
Gly Glu
<210> 54
<211> 84
<212> PRT
<213> Homo sapiens
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55

50

35

50

```
Ser Pro Leu Lys Ser Asn Ser Asp Ser Ala Arg Leu Pro Ile Ser
                  65
                                      70
 Ser Gly Ser Thr Ser Ser Ser Arg Ile
                  80
 <210> 55
 <211> 97
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc feature
.<223> Incyte Clone No: 2779436
Met Gln Leu Gly Thr Gly Leu Leu Leu Ala Ala Val Leu Ser Leu
                                      10
Gln Leu Ala Ala Glu Ala Ile Trp Cys His Gln Cys Thr Gly
                  20
                                      25
Phe Gly Gly Cys Ser His Gly Ser Arg Cys Leu Arg Asp Ser Thr
                  35
                                      40
His Cys Val Thr Thr Ala Thr Arg Val Leu Ser Asn Thr Glu Asp
                  50
                                      55
Leu Pro Leu Val Thr Lys Met Cys His Ile Gly Cys Pro Asp Ile
                 65
                                      70
Pro Ser Leu Gly Leu Gly Pro Tyr Val Ser Ile Ala Cys Cys Gln
                 80
                                      85
Thr Ser Leu Cys Asn His Asp
<210> 56
<211> 140
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2808528
<400> 56
Met Ala Ala Ser Leu Gly Gln Val Leu Ala Leu Val Leu Val Ala
                                     10
Ala Leu Trp Gly Gly Thr Gln Pro Leu Leu Lys Arg Ala Ser Ala
                                     25
Gly Leu Gln Arg Val His Glu Pro Thr Trp Ala Gln Gln Leu Leu
```

40

55

70

Gln Glu Met Lys Thr Leu Phe Leu Asn Thr Glu Tyr Leu Met Pro

Phe Leu Leu Asn Gln Cys Gly Ser Leu Leu Tyr Tyr Leu Thr Leu

<210> 57
<211> 285
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2809230

<400> 57 Met Glu Val Pro Pro Pro Ala Pro Arg Ser Phe Leu Cys Arg Ala 10 Leu Cys Leu Phe Pro Arg Val Phe Ala Ala Glu Ala Val Thr Ala 20 Asp Ser Glu Val Leu Glu Glu Arg Gln Lys Arg Leu Pro Tyr Val 35 40 Pro Glu Pro Tyr Tyr Pro Glu Ser Gly Trp Asp Arg Leu Arg Glu 50 55 Leu Phe Gly Lys Asp Glu Gln Gln Arg Ile Ser Lys Asp Leu Ala 65 70 Asn Ile Cys Lys Thr Ala Ala Thr Ala Gly Ile Ile Gly Trp Val 80 85 Tyr Gly Gly Ile Pro Ala Phe Ile His Ala Lys Gln Gln Tyr Ile 95 100 Glu Gln Ser Gln Ala Glu Ile Tyr His Asn Arg Phe Asp Ala Val 110 115 Gln Ser Ala His Arg Ala Ala Thr Arg Gly Phe Ile Arg Tyr Gly 125 130 Trp Arg Trp Gly Trp Arg Thr Ala Val Phe Val Thr Ile Phe Asn 140 145 Thr Val Asn Thr Ser Leu Asn Val Tyr Arg Asn Lys Asp Ala Leu 155 160 Ser His Phe Val Ile Ala Gly Ala Val Thr Gly Ser Leu Phe Arg 170 175 Ile Asn Val Gly Leu Arg Gly Leu Val Ala Gly Gly Ile Ile Gly 185 190 Ala Leu Leu Gly Thr Pro Val Gly Gly Leu Leu Met Ala Phe Gln 200 205 Lys Tyr Ser Gly Glu Thr Val Gln Glu Arg Lys Gln Lys Asp Arg 215 220

Lys Ala Leu His Glu Leu Lys Leu Glu Glu Trp Lys Gly Arg Leu

Gln Val Thr Glu His Leu Pro Glu Lys Ile Glu Ser Ser Leu Gln

230

250

265

280

Glu Asp Glu Pro Glu Asn Asp Ala Lys Lys Ile Glu Ala Leu Leu

Asn Leu Pro Arg Asn Pro Ser Val Ile Asp Lys Gln Asp Lys Asp

245

260

275

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<210> 58
 <211> 262
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
<223> Incyte Clone No: 2816821
<400> 58
Met Thr Gln Pro Val Pro Arg Leu Ser Val Pro Ala Ala Leu Ala
                                      10
Leu Gly Ser Ala Ala Leu Gly Ala Ala Phe Ala Thr Gly Leu Phe
Leu Gly Arg Arg Cys Pro Pro Trp Arg Gly Arg Arg Glu Gln Cys
Leu Leu Pro Pro Glu Asp Ser Arg Leu Trp Gln Tyr Leu Leu Ser
                 50
                                     55
Arg Ser Met Arg Glu His Pro Ala Leu Arg Ser Leu Arg Leu Leu
                 65
                                     70
Thr Leu Glu Gln Pro Gln Gly Asp Ser Met Met Thr Cys Glu Gln
                 80
                                     85
Ala Gln Leu Leu Ala Asn Leu Ala Arg Leu Ile Gln Ala Lys Lys
                 95
                                    100
Ala Leu Asp Leu Gly Thr Phe Thr Gly Tyr Ser Ala Leu Ala Leu
                110
                                    115
Ala Leu Ala Leu Pro Ala Asp Gly Arg Val Val Thr Cys Glu Val
                125
                                    130
Asp Ala Gln Pro Pro Glu Leu Gly Arg Pro Leu Trp Arg Gln Ala
                140
                                    145
Glu Ala Glu His Lys Ile Asp Leu Arg Leu Lys Pro Ala Leu Glu
                155
                                    160
Thr Leu Asp Glu Leu Leu Ala Ala Gly Glu Ala Gly Thr Phe Asp
                170
                                    175
Val Ala Val Val Asp Ala Asp Lys Glu Asn Cys Ser Ala Tyr Tyr
                185
                                    190
Glu Arg Cys Leu Gln Leu Leu Arg Pro Gly Gly Ile Leu Ala Val
                200
                                    205
Leu Arg Val Leu Trp Arg Gly Lys Val Leu Gln Pro Pro Lys Gly
                215
                                    220
Asp Val Ala Ala Glu Cys Val Arg Asn Leu Asn Glu Arg Ile Arg
               230
                                    235
Arg Asp Val Arg Val Tyr Ile Ser Leu Leu Pro Leu Gly Asp Gly
               245
Leu Thr Leu Ala Phe Lys Ile
               260
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<210> 59
<211> 189
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2817268
<400> 59
Met Ala Leu Leu Ser Arg Pro Ala Leu Thr Leu Leu Leu Leu
                  5
                                     10
Met Ala Ala Val Val Arg Cys Gln Glu Gln Ala Gln Thr Thr Asp
                 20
                                     25
Trp Arg Ala Thr Leu Lys Thr Ile Arg Asn Gly Val His Lys Ile
                 35
                                     40
Asp Thr Tyr Leu Asn Ala Ala Leu Asp Leu Leu Gly Glu Asp
                 50
                                     55
Gly Leu Cys Gln Tyr Lys Cys Ser Asp Gly Ser Lys Pro Phe Pro
                 65
                                     70
Arg Tyr Gly Tyr Lys Pro Ser Pro Pro Asn Gly Cys Gly Ser Pro
                 80
                                     85
Leu Phe Gly Val His Leu Asn Ile Gly Ile Pro Ser Leu Thr Lys
                 95
                                    100
Cys Cys Asn Gln His Asp Arg Cys Tyr Glu Thr Cys Gly Lys Ser
                110
                                    115
Lys Asn Asp Cys Asp Glu Glu Phe Gln Tyr Cys Leu Ser Lys Ile
                125
                                    130
Cys Arg Asp Val Gln Lys Thr Leu Gly Leu Thr Gln His Val Gln
                140
                                   145
Ala Cys Glu Thr Thr Val Glu Leu Leu Phe Asp Ser Val Ile His
                155
                                   160
Leu Gly Cys Lys Pro Tyr Leu Asp Ser Gln Arg Ala Ala Cys Arg
                170
                                    175
Cys His Tyr Glu Glu Lys Thr Asp Leu
                185
<210> 60
<211> 257
<212> PRT
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Leu Leu Ile Ser Ser Leu Val Trp Phe Met Ala Arg Val Ile Ile
                 50
                                     55
Asp Asn Lys Asp Gly Pro Thr Gln Lys Tyr Leu Leu Ile Phe Gly
                 65
                                     70
                                                          75
Ala Phe Val Ser Val Tyr Ile Gln Glu Met Phe Arg Phe Ala Tyr
                 80
                                                          90
Tyr Lys Leu Leu Lys Lys Ala Ser Glu Gly Leu Lys Ser Ile Asn
                 95
                                    100
Pro Gly Glu Thr Ala Pro Ser Met Arg Leu Leu Ala Tyr Val Ser
                110
                                    115
Gly Leu Gly Phe Gly Ile Met Ser Gly Val Phe Ser Phe Val Asn
                125
                                    130
Thr Leu Ser Asp Ser Leu Gly Pro Gly Thr Val Gly Ile His Gly
                140
                                    145
Asp Ser Pro Gln Phe Phe Leu Tyr Ser Ala Phe Met Thr Leu Val
                155
                                    160
                                                        165
Ile Ile Leu Leu His Val Phe Trp Gly Ile Val Phe Phe Asp Gly
                170
Cys Glu Lys Lys Trp Gly Ile Leu Leu Ile Val Leu Leu Thr
                185
                                                        195
His Leu Leu Val Ser Ala Gln Thr Phe Ile Ser Ser Tyr Tyr Gly
                200
Ile Asn Leu Ala Ser Ala Phe Ile Ile Leu Val Leu Met Gly Thr
                215
                                    220
Trp Ala Phe Leu Ala Ala Gly Gly Ser Cys Arg Ser Leu Lys Leu
                230
                                    235
Cys Leu Leu Cys Gln Asp Lys Asn Phe Leu Leu Tyr Asn Gln Arg
               245
                                   250
                                                        255
Ser Arg
```

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<210> 61
<211> 82
<212> PRT
<213> Homo sapiens
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<221> misc_feature
<223> Incyte Clone No: 2949822
Met Pro Phe Ser Trp Met Val Ile Ile Leu Gly Phe Leu Cys Gly
                                     10
Leu Ser Gly Gln Leu Gln Ile Met Asn Thr Leu Ser Ser Leu Pro
                 20
Ile Val Leu Leu Val Ser Ser Ser Cys Leu Ile Leu Ala Arg Met
                 35
Ser Tyr Ser Ile Leu Thr Ser Ser Tyr Gly Gly Val Phe Ile
                 50
Leu Leu Asp Leu Lys Arg Asn Thr Ser Lys Val Ser Pro Leu Met
                 65
                                     70
Met Met Phe Ala Ile Gly His
```

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<210> 62
 <211> 202
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte Clone No: 2992192
 <400> 62
Met Ala Ala Pro Trp Arg Arg Trp Pro Thr Gly Leu Leu Ala Val
                                      10
Leu Arg Pro Leu Leu Thr Cys Arg Pro Leu Gln Gly Thr Thr Leu
                  20
Gln Arg Asp Val Leu Leu Phe Glu His Asp Arg Gly Arg Phe Phe
                                      40
Thr Ile Leu Gly Leu Phe Cys Ala Gly Gln Gly Val Phe Trp Ala
                  50
Ser Met Ala Val Ala Val Ser Arg Pro Pro Val Pro Val Gln
                  65
                                      70
Pro Leu Asp Ala Glu Val Pro Asn Arg Gly Pro Phe Asp Leu Arg
                                      85
                                                          90
Ser Ala Leu Trp Arg Tyr Gly Leu Ala Val Gly Cys Gly Ala Ile
                                     100
Gly Ala Leu Val Leu Gly Ala Gly Leu Leu Phe Ser Leu Arg Ser
                                     115
Val Arg Ser Val Val Leu Arg Ala Gly Gly Gln Gln Val Thr Leu
                125
                                     130
                                                         135
Thr Thr His Ala Pro Phe Gly Leu Gly Ala His Phe Thr Val Pro
                140
                                     145
Leu Lys Gln Val Ser Cys Met Ala His Arg Gly Glu Val Pro Ala
                155
                                    160
Met Leu Pro Leu Lys Val Lys Gly Arg Arg Phe Tyr Phe Leu Leu
                170
                                    175
Asp Lys Thr Gly His Phe Pro Asn Thr Lys Leu Phe Asp Asn Thr
                185
                                    190
Val Gly Ala Tyr Arg Ser Leu
                200
<210> 63
<211> 450
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2992458
<400> 63
Met Leu Val Thr Ala Tyr Leu Ala Phe Val Gly Leu Leu Ala Ser
                 5
                                     10
Cys Leu Gly Leu Glu Leu Ser Arg Cys Arg Ala Lys Pro Pro Gly
```

```
Arg Ala Cys Ser Asn Pro Ser Phe Leu Arg Phe Gln Leu Asp Phe
                  35
 Tyr Gln Val Tyr Phe Leu Ala Leu Ala Ala Asp Trp Leu Gln Ala
                  50
 Pro Tyr Leu Tyr Lys Leu Tyr Gln His Tyr Tyr Phe Leu Glu Gly
                                       70
 Gln Ile Ala Ile Leu Tyr Val Cys Gly Leu Ala Ser Thr Val Leu
 Phe Gly Leu Val Ala Ser Ser Leu Val Asp Trp Leu Gly Arg Lys
                  95
 Asn Ser Cys Val Leu Phe Ser Leu Thr Tyr Ser Leu Cys Cys Leu
                 110
 Thr Lys Leu Ser Gln Asp Tyr Phe Val Leu Leu Val Gly Arg Ala
                 125
 Leu Gly Gly Leu Ser Thr Ala Leu Leu Phe Ser Ala Phe Glu Ala
                 140
 Trp Tyr Ile His Glu His Val Glu Arg His Asp Phe Pro Ala Glu
                 155
 Trp Ile Pro Ala Thr Phe Ala Arg Ala Ala Phe Trp Asn His Val
                 170
 Leu Ala Val Val Ala Gly Val Ala Ala Glu Ala Val Ala Ser Trp
                 185
 Ile Gly Leu Gly Pro Val Ala Pro Phe Val Ala Ala Ile Pro Leu
                 200
Leu Ala Leu Ala Gly Ala Leu Ala Leu Arg Asn Trp Gly Glu Asn
                 215
                                     220
                                                         225
Tyr Asp Arg Gln Arg Ala Phe Ser Arg Thr Cys Ala Gly Gly Leu
                 230
                                     235
Arg Cys Leu Leu Ser Asp Arg Val Leu Leu Gly Thr Ile
                 245
                                     250
Gln Ala Leu Phe Glu Ser Val Ile Phe Ile Phe Val Phe Leu Trp
                260
                                     265
Thr Pro Val Leu Asp Pro His Gly Ala Pro Leu Gly Ile Ile Phe
                275
                                     280
Ser Ser Phe Met Ala Ala Ser Leu Leu Gly Ser Ser Leu Tyr Arg
                290
                                     295
Ile Ala Thr Ser Lys Arg Tyr His Leu Gln Pro Met His Leu Leu
                305
                                    310
Ser Leu Ala Val Leu Ile Val Val Phe Ser Leu Phe Met Leu Thr
                320
                                    325
Phe Ser Thr Ser Pro Gly Gln Glu Ser Pro Val Glu Ser Phe Ile
                335
                                    340
Ala Phe Leu Leu Ile Glu Leu Ala Cys Gly Leu Tyr Phe Pro Ser
                350
                                    355
Met Ser Phe Leu Arg Arg Lys Val Ile Pro Glu Thr Glu Gln Ala
                365
                                    370
Gly Val Leu Asn Trp Phe Arg Val Pro Leu His Ser Leu Ala Cys
                380
                                    385
Leu Gly Leu Leu Val Leu His Asp Ser Asp Arg Lys Thr Gly Thr
                395
                                    400
Arg Asn Met Phe Ser Ile Cys Ser Ala Val Met Val Met Ala Leu
                410
                                    415
Leu Ala Val Val Gly Leu Phe Thr Val Val Arg His Asp Ala Glu
                425
                                    430
Leu Arg Val Pro Ser Pro Thr Glu Glu Pro Tyr Ala Pro Glu Leu
                440
                                    445
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<210> 64
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 <213> Homo sapiens
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 <221> misc_feature
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 <400> 64
 Met Ala Arg Cys Phe Ser Leu Val Leu Leu Leu Thr Ser Ile Trp
 Thr Thr Arg Leu Leu Val Gln Gly Ser Leu Arg Ala Glu Glu Leu
                  20
 Ser Ile Gln Val Ser Cys Arg Ile Met Gly Ile Thr Leu Val Ser
                  35
                                      40
 Lys Lys Ala Asn Gln Gln Leu Asn Phe Thr Glu Ala Lys Glu Ala
                  50
 Cys Arg Leu Leu Gly Leu Ser Leu Ala Gly Lys Asp Gln Val Glu
                 65
Thr Ala Leu Lys Ala Ser Phe Glu Thr Cys Ser Tyr Gly Trp Val
                 80
                                     85
Gly Asp Gly Phe Val Val Ile Ser Arg Ile Ser Pro Asn Pro Lys
                 95
                                    100
Cys Gly Lys Asn Gly Val Gly Val Leu Ile Trp Lys Val Pro Val
                110
                                   115
Ser Arg Gln Phe Ala Ala Tyr Cys Tyr Asn Ser Ser Asp Thr Trp
                125
                                    130
Thr Asn Ser Cys Ile Pro Glu Ile Ile Thr Thr Lys Asp Pro Ile
                140
                                    145
Phe Asn Thr Gln Thr Ala Thr Gln Thr Thr Glu Phe Ile Val Ser
                155
                                    160
Asp Ser Thr Tyr Ser Val Ala Ser Pro Tyr Ser Thr Ile Pro Ala
                170
                                    175
Pro Thr Thr Pro Pro Ala Pro Ala Ser Thr Ser Ile Pro Arg
                185
                                    190
Arg Lys Lys Leu Ile Cys Val Thr Glu Val Phe Met Glu Thr Ser
                200
                                    205
Thr Met Ser Thr Glu Thr Glu Pro Phe Val Glu Asn Lys Ala Ala
                215
                                    220
Phe Lys Asn Glu Ala Ala Gly Phe Gly Gly Val Pro Thr Ala Leu
                230
                                    235
Leu Val Leu Ala Leu Leu Phe Phe Gly Ala Ala Gly Leu Gly
                245
                                    250
Phe Cys Tyr Val Lys Arg Tyr Val Lys Ala Phe Pro Phe Thr Asn
                260
                                    265
Lys Asn Gln Gln Lys Glu Met Ile Glu Thr Lys Val Val Lys Glu
                275
                                   280
Glu Lys Ala Asn Asp Ser Asn Pro Asn Glu Glu Ser Lys Lys Thr
               290
                                   295
Asp Lys Asn Pro Glu Glu Ser Lys Ser Pro Ser Lys Thr Thr Val
               305
                                   310
Arg Cys Leu Glu Ala Glu Val
               320
```

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<210> 65
 <211> 104
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte Clone No: 3120415
 <400> 65
Met Lys Leu Ala Ala Leu Leu Gly Leu Cys Val Ala Leu Ser Cys
                                      10
Ser Ser Ala Ala Ala Phe Leu Val Gly Ser Ala Lys Pro Val Ala
                                      25
Gln Pro Val Ala Ala Leu Glu Ser Ala Ala Glu Ala Gly Ala Gly
                                      40
Thr Leu Ala Asn Pro Leu Gly Thr Leu Asn Pro Leu Lys Leu Leu
                                     55
Leu Ser Ser Leu Gly Ile Pro Val Asn His Leu Ile Glu Gly Ser
                  65
                                     70
Gln Lys Cys Val Ala Glu Leu Gly Pro Gln Ala Val Gly Ala Val
                  80
                                     85
Lys Ala Leu Lys Ala Leu Leu Gly Ala Leu Thr Val Phe Gly
                  95
<210> 66
<211> 93
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 126758
<400> 66
Met Lys Leu Val Thr Ile Phe Leu Leu Val Thr Ile Ser Leu Cys
                 5
                                     10
Ser Tyr Ser Ala Thr Ala Phe Leu Ile Asn Lys Val Pro Leu Pro
                 20
Val Asp Lys Leu Ala Pro Leu Pro Leu Asp Asn Ile Leu Pro Phe
                35
                                     40
Met Asp Pro Leu Lys Leu Leu Lys Thr Leu Gly Ile Ser Val
                 50
Glu His Leu Val Glu Gly Leu Arg Lys Cys Val Asn Glu Leu Gly
                                     70
```

Pro Glu Ala Ser Glu Ala Val Lys Lys Leu Leu Glu Ala Leu Ser

His Leu Val

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<210> 67
 <211> 71
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte Clone No: 674760
 <400> 67
Met Thr Ala Gly Gln Phe Pro Ala Leu Val Ser Leu Ala Leu Leu
                                      10
Leu Asp Gly Gly Arg Arg Ala Ser Ala Arg Arg Asn Arg Gly His
                  20
Leu Trp Val Phe Cys Thr Ser Phe Leu Leu Ala Pro Trp Glu Val
Glu Asp Val Gly Trp Lys Lys Gly Leu Asp Leu Pro Pro Ser Ser
Ser Pro Pro Ser Pro Lys Glu Leu Ala Leu Gln
<210> 68
<211> 394
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1229438
<400> 68
Met Lys Arg Gln Asn Val Arg Thr Leu Ala Leu Ile Val Cys Thr
                  5
Phe Thr Tyr Leu Leu Val Gly Ala Ala Val Phe Asp Ala Leu Glu
                 20
Ser Glu Pro Glu Leu Ile Glu Arg Gln Arg Leu Glu Leu Arg Gln
                 35
Gln Glu Leu Arg Ala Arg Tyr Asn Leu Ser Gln Gly Gly Tyr Glu
                 50
Glu Leu Glu Arg Val Val Leu Arg Leu Lys Pro His Lys Ala Gly
                 65
                                     70
Val Gln Trp Arg Phe Ala Gly Ser Phe Tyr Phe Ala Ile Thr Val
                 80
                                     85
Ile Thr Thr Ile Gly Tyr Gly His Ala Ala Pro Ser Thr Asp Gly
                 95
                                    100
Gly Lys Val Phe Cys Met Phe Tyr Ala Leu Leu Gly Ile Pro Leu
                110
                                    115
Thr Leu Val Met Phe Gln Ser Leu Gly Glu Arg Ile Asn Thr Leu
                                    130
```

Val Arg Tyr Leu Leu His Arg Ala Lys Lys Gly Leu Gly Met Arg

Arg Ala Asp Val Ser Met Ala Asn Met Val Leu Ile Gly Phe Phe

Ser Cys Ile Ser Thr Leu Cys Ile Gly Ala Ala Phe Ser His

```
170
                                    175
Tyr Glu His Trp Thr Phe Phe Gln Ala Tyr Tyr Cys Phe Ile
                185
                                    190
Thr Leu Thr Thr Ile Gly Phe Gly Asp Tyr Val Ala Leu Gln Lys
                200
                                    205
                                                       210
Asp Gln Ala Leu Gln Thr Gln Pro Gln Tyr Val Ala Phe Ser Phe
                215
                                    220
Val Tyr Ile Leu Thr Gly Leu Thr Val Ile Gly Ala Phe Leu Asn
                230
Leu Val Val Leu Arg Phe Met Thr Met Asn Ala Glu Asp Glu Lys
                245
Arg Asp Ala Glu His Arg Ala Leu Leu Thr Arg Asn Gly Gln Ala
                260
Gly Gly Gly Gly Gly Gly Ser Ala His Thr Thr Asp Thr Ala
                275
Ser Ser Thr Ala Ala Ala Gly Gly Gly Phe Arg Asn Val Tyr
                290
Ala Glu Val Leu His Phe Gln Ser Met Cys Ser Cys Leu Trp Tyr
               305
                                   310
Lys Ser Arg Glu Lys Leu Gln Tyr Ser Ile Pro Met Ile Ile Pro
               320
                                   325
Arg Asp Leu Ser Thr Ser Asp Thr Cys Val Glu Gln Ser His Ser
               335
Ser Pro Gly Gly Gly Arg Tyr Ser Asp Thr Pro Ser Arg Arg
Cys Leu Cys Ser Gly Ala Pro Arg Ser Ala Ile Ser Ser Val Ser
                                   370
Thr Gly Leu His Ser Leu Ser Thr Phe Arg Gly Leu Met Lys Arg
                                   385
Arg Ser Ser Val
```

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<210> 70
 <211> 71
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc feature
 <223> Incyte Clone No: 1359283
 <400> 70
 Met Arg Leu Thr Gly Leu Thr Leu Leu Ser Leu Met Glu Ser
                                     10
 Leu Gly Gln Val Glu Asp Arg Phe Phe Ser Thr His Arg Arg Phe
                                      25
 Pro His His Thr Pro Ile Ser Gly Leu Leu Cys Arg Glu Phe Ser
                                      40
Leu Pro Lys Arg Ser Gly Val Pro Trp Thr Arg Val Leu Ile Ser
                                      55
 Cys Ile Trp Arg Ser Gly Ala Gly Lys Arg Met
<210> 71
<211> 247
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1450703
<400> 71
Met His Leu Ala Arg Leu Val Gly Ser Cys Ser Leu Leu Leu
                                     10
Leu Gly Ala Leu Ser Gly Trp Ala Ala Ser Asp Asp Pro Ile Glu
                 20
Lys Val Ile Glu Gly Ile Asn Arg Gly Leu Ser Asn Ala Glu Arg
                 35
Glu Val Gly Lys Ala Leu Asp Gly Ile Asn Ser Gly Ile Thr His
                 50
Ala Gly Arg Glu Val Glu Lys Val Phe Asn Gly Leu Ser Asn Met
                 65
Gly Ser His Thr Gly Lys Glu Leu Asp Lys Gly Val Gln Gly Leu
                 80
Asn His Gly Met Asp Lys Val Ala His Glu Ile Asn His Gly Ile
                95
```

Asn Ala Ala Gly Gln Ala Gly Lys Glu Ala Asp Lys Ala Val Gln 125 130 Gly Phe His Thr Gly Val His Gln Ala Gly Lys Glu Ala Glu Lys 140 145 Leu Gly Gln Gly Val Asn His Ala Ala Asp Gln Ala Gly Lys Glu 155 Val Glu Lys Leu Gly Gln Gly Ala His His Ala Ala Gly Gln Ala

Gly Gln Ala Gly Lys Glu Ala Glu Lys Leu Gly His Gly Val Asn

110

```
170
                                   175
Gly Lys Glu Leu Gln Asn Ala His Asn Gly Val Asn Gln Ala Ser
                185
                                   190
Lys Glu Ala Asn Gln Leu Leu Asn Gly Asn His Gln Ser Gly Ser
                200
                                   205
                                                       210
Ser Ser His Gln Gly Gly Ala Thr Thr Pro Leu Ala Ser Gly
                215
                                   220
Ala Ser Val Asn Thr Pro Phe Ile Asn Leu Pro Ala Leu Trp Arg
               230
                                   235
                                                       240
Ser Val Ala Asn Ile Met Pro
               245
```

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<210> 72
<211> 73
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1910668
<400> 72
Met Thr Cys Trp Met Leu Pro Pro Ile Ser Phe Leu Ser Tyr Leu
                                     10
Pro Leu Trp Leu Gly Pro Ile Trp Pro Cys Ser Gly Ser Thr Leu
                                     25
Gly Lys Pro Asp Pro Gly Val Trp Pro Ser Leu Phe Arg Pro Trp
                 35
                                     40
Asp Ala Ala Ser Pro Gly Asn Tyr Ala Leu Ser Arg Gly Glu Asn
Gln Tyr Glu Lys Trp Gly Gln Gly Thr His Ser Ser Leu
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<210> 73 <211> 70 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1955143 <400> 73 Met Gly Arg Leu Arg Tyr Phe Phe Ser Leu Leu Leu Arg Trp 5 10 Gly Gln Leu Leu Gly Ala Asp Glu Phe Cys Cys His Lys Ser Tyr 20 25 Ile Ala His Leu Val Cys Thr Glu Ser Ala Ile Leu Asn Pro Gly 35 40 His Ala Leu Glu Leu Tyr Lys Lys Asn Leu Gln Val Ser Ile Leu 50

Ser Pro Tyr Pro Thr Asp Pro Ile His Leu 65 70

<210> 74 <211> 67 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1961637 <400> 74 Met Met Phe Thr Ser Leu Ser Leu Ala Leu Pro Phe Leu Leu Gln 10 Thr Met Leu Cys Leu Arg Ala Leu Leu Ile Ala Val Pro His Gly 20 25 His Asp Trp Asn Arg Asp Ala Thr Ser Phe Tyr Thr Ser Thr Val 40 Ser Trp Val Lys Ser Phe Phe Leu Phe Val Leu Asp Gly Val Ser 50 55 Leu Leu Pro Arg Leu Glu 65

<210> 75 <211> 91 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 1990762 <400> 75 Met Trp Pro Thr Trp Ala Trp Ser Trp Val Gln Thr Leu Thr 10 Leu Ala Leu Leu Ile Ser Cys Val Thr Leu Gly Gln Leu Ile Thr 25 Thr Leu Gln Val Ser Phe Leu Ile Cys Glu Met Asp Val Ile Ile 35 40 Gly Cys Asp Glu Met Ile Pro Ser Glu Ser Leu Val Leu Leu Trp 50 55 Pro Pro Pro Leu Leu Leu Gly Glu Phe Trp Ile Trp Asn Pro 65 70 Val Ser Arg Ile Leu Phe Trp Leu Cys His Val Pro Ala Gly Gln 80 85 Leu

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<211> 56
 <212> PRT
 <213> Homo sapiens
 <220>
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 <223> Incyte Clone No: 1994131
 <400> 76
 Met Asn Glu Trp Trp Leu Leu Leu Leu His Leu His Pro Pro
                                      10
Arg Val Ile Ser Pro Phe Trp Phe Ile Val Ser Val Leu Thr Ala
                  20
                                      25
 Cys Asp Asn Arg Lys Tyr Ile Leu Leu Arg Thr Val Pro Val Phe
                  35
                                     40
Ser Phe Pro Glu Asn Thr Tyr Phe Asp Val Gly
<210> 77
<211> 112
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 1997745
<400> 77
Met Pro Leu Phe Leu Ser Ile Pro Ser Leu Phe Leu Thr Leu Ser
Gly Leu Gly Leu Ala Val Gln Ser Pro Ala Gly Gly Cys Trp Gly
Leu Ser Leu Cys Arg His Cys Val Phe Leu Arg Gly Cys Pro Gln
Asn Thr Pro Pro Ala Pro Trp Gly Ser Ser Gly Ser His Phe Ser
Trp Ser Leu Arg Ser Gln Lys Gln Leu Leu Gln Glu Ala Lys Lys
                                     70
                                                         75
Arg Leu Gly Trp Leu Leu Val Leu Met Met Ala Phe Ile Leu Leu
                 80
Gly His Phe Gly Tyr Ile His Gly His Cys Phe His Leu Ser Phe
                 95
                                   100
Leu Pro Val Pro Pro Leu Pro
                110
```

<210> 78 <211> 54 <212> PRT

<210> 76

<213> Homo sapiens

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<220>
 <221> misc feature
 <223> Incyte Clone No: 2009035
 <400> 78
Met Met Leu Gln Pro Val Asp Leu Leu Gln Ser Tyr Leu Leu Leu
                  5
                                      10
Leu Tyr Cys Trp Ser Phe Ser Leu Leu Phe Thr Leu Leu Cys Asn
                 20
                                      25
Ala Val Arg Asn Asp Phe Phe His Lys Leu Phe Ser Ile Tyr Trp
                 35
Met Tyr Asn Leu Thr His Ser Lys His
                 50
<210> 79
<211> 57
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2009152
<400> 79
Met Lys Phe Tyr Ala Val Leu Leu Ser Ile Cys Leu Leu Leu Ser
 1
                  5
                                     10
Cys Trp Cys Ala Cys His Val Arg Asp Cys Asn Leu Ile Cys Leu
                                     25
Phe Ser Thr Val Lys Ala Ile Thr Arg Glu Leu Leu Gln Leu Pro
                 35
                                     40
Ser Tyr Val Lys Arg Phe Phe Phe Asn Ser Leu Arg
                 50
<210> 80
<211> 52
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2061752
<400> 80
Met Gln Arg Leu Gly Lys Ala Pro Gly Thr Trp Gln Ala Ile Ser
1
                                    10
Lys Cys Trp Leu Leu Leu Leu Ser Leu Pro Phe Ser Gln Ser
                 20
                                     25
Ile Ile Ile Ser Leu Arg Ala Gly Thr Met Ser Tyr Leu Pro Leu
                 35
Tyr Phe Pro Gln Tyr Phe Pro
                50
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<210> 81
 <211> 64
 <212> PRT
 <213> Homo sapiens
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 <221> misc_feature
 <223> Incyte Clone No: 2061933
 <400> 81
 Met Lys Leu Leu Leu Lys Leu Asp Phe Phe Ile Leu Leu Gly
  1
                  5
                            . 10
 Ser Glu Glu Ser Arg Cys Leu Val Asp Val Gln Tyr Val Ile Phe
                                     25
 Phe Leu Ile Glu Cys Val His Leu Lys Ser Ser Leu Thr Phe Leu
                                     40
 Glu Arg Leu Leu Ser Ile Asn Asn Gly Ile Leu Glu Glu Lys Trp
 Phe Phe Lys Ser
<210> 82
<211> 65
 <212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2081422
<400> 82
Met Lys Pro Leu Ile Pro Phe Leu Ser Pro Pro Pro Leu Leu Pro
                                    10
Leu Thr Phe Phe Leu Ser Ser Leu Leu Leu Ser Pro Leu Cys Arg
                 20
                                     25
Ala Leu Gly Thr Ser Gln Ala Val Pro Pro Leu Arg Ala Leu Ser
                                    40
Val Thr Asp Ala His Gly Ser Leu Leu Leu His Pro Lys Thr Leu
Ala Cys Pro Cys Leu
<210> 83
<211> 56
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
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<223> Incyte Clone No: 2101278

<400> 83

<210> 84 <211> 120 <212> PRT <213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2121353

<400> 84

Met Pro Ala Leu Pro Pro Gly Phe Ser Gln Ala Gly Ser Cys Val 5 Pro Thr Gly Ser Ser Leu Val Leu Cys Leu Leu Ala Ala Ser Leu 20 Leu Leu Phe Val Pro Thr Leu Ala Leu Leu Thr Gly Ala Thr Thr 35 40 Cys Trp Cys Leu His Asn Lys Arg Leu Ala Leu Arg Pro Leu Ala 55 Trp Gln Gly Leu Trp Gly Leu Val Ser Thr Arg Leu Ser His Gly 65 70 Arg Thr Ser Phe Tyr Phe Asn Ser Leu Pro Leu Gln Thr Asn Ser 80 85 Ser Thr Cys Gln Asn His Ser Trp Asp Ser Gly Ala Arg Ala Thr 95 100 Ala Leu Ala Ser Gly Arg Thr Gln Glu Gly Gly Val Gly Ser Val 110 115

<210> 86 <211> 62

<210> 87 <211> 75 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 2295344 <400> 87 Met Met Ile Leu Leu Ser Leu Leu Val Ala Leu Ile Ser Val Ser 5 10 Leu Val Phe Leu Gly Leu Val Arg Phe Ser Arg Glu Asp Phe Ser Phe Pro Leu Trp Arg Glu Lys Ala Phe Tyr Gln His Ser Ser Ser 40 Ser Val Gly Glu Arg Leu Gln Ala Leu Arg Lys His Ala Phe Thr 55 Leu Phe Gly Thr Ile Pro Leu Leu Val Thr Val Pro Gln Val Pro

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<210> 88
<211> 80
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2303994
<400> 88
Met Asn Ser Ile Phe Phe Leu Ser Leu Cys Leu Pro Leu Trp Val
                                      10
Ser Leu Leu Trp Ala Lys Pro Leu Glu Met His Lys Thr Ser Arg
                 20
                                      25
His Gly Phe Trp Gln Lys Leu His Asp Phe Lys Leu Ala Leu Leu
                 35
                                      40
Leu Leu Thr Phe His Arg Glu Lys Ile Phe Pro Leu Lys Lys Thr
Gly Leu Val Ile Phe Ser Leu Val Ala Leu Ser Arg Asp Ile Ser
Ala Leu His Tyr Thr
<210> 89
<211> 50
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2497805
<400> 89
Met Arg Pro Ala Arg Leu Gly Pro Arg Cys Ser Asp Leu Asp Phe
                  5
                                     10
Gly Leu Val Leu Ser Ser Trp Leu Arg Leu Ala Arg Cys Pro Leu
Glu Ser Ser Phe Gly Phe Ala Phe Phe Val Cys Leu Phe Ser Pro
                 35
                                     40
Asn Phe Cys Gln Thr
<210> 90
<211> 116
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2646362
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<400> 90 Met Trp Trp Ala Leu Cys Ser Met Leu Pro Leu Leu Gly Cys Ala 10 Cys Ser Ser Gly Cys Trp Gly Ser Gly Pro Thr Pro Leu Leu Ala 20 25 Glu Pro Thr Phe Leu Cys Val Ser Ser Arg Pro His Asn Pro Leu 35 40 Ser Phe Leu Ser Val Leu Pro Cys Ser Arg Gly Pro Gly Pro Ser 50 55 Gly Leu Gln Gly Asp Gly Ala Gly Leu Pro Ala His Leu Gly Pro 65 70 Leu Ser Cys Ile Cys Leu Pro Ser Leu Leu Cys Asp Leu Gly Glu 80 85 Arg Gln Cys Pro Leu Trp Ala Val Arg Ser Thr Gln Cys Leu Ile 95 100 Ala Gly Lys Lys Val Leu Gln Arg Leu Cys Pro 110 <210> 91 <211> 67 <212> PRT <213> Homo sapiens <220> <221> misc feature <223> Incyte Clone No: 2657146 <400> 91 Met Ile Cys Gln Cys Leu Arg Leu Leu Leu Val Leu Val Thr Leu Leu Ile Cys Phe Ser Pro Asp Arg Leu Thr Cys Pro Leu Asn Ser 20 Ala Val Val Leu Ala Ser Tyr Ala Val Gln Cys Lys Ser Gln Arg 35 40 Glu His Phe Thr Asp Gly Gln Val Val Leu Ile Ser Val Trp Arg 50 Lys Ser Leu Val Pro Pro Ala 65 <210> 92 <211> 538 <212> PRT

<211> 538
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2755786

<400> 92
Met Ala Gly Ala Arg Ala Ala Ala Ala Ala Ser Ala Gly Ser
1 5 10 15

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Ser Ala Ser Ser Gly Asn Gln Pro Pro Gln Glu Leu Gly Leu Gly
                                      25
 Glu Leu Leu Glu Glu Phe Ser Arg Thr Gln Tyr Arg Ala Lys Asp
                                      40
 Gly Ser Gly Thr Gly Gly Ser Lys Val Glu Arg Ile Glu Lys Arg
                                      55
 Cys Leu Glu Leu Phe Gly Arg Asp Tyr Cys Phe Ser Val Ile Pro
                  65
                                      70
 Asn Thr Asn Gly Asp Ile Cys Gly His Tyr Pro Arg His Ile Val
                  80
                                      85
 Phe Leu Glu Tyr Glu Ser Ser Glu Lys Glu Lys Asp Thr Phe Glu
                  95
                                     100
 Ser Thr Val Gln Val Ser Lys Leu Gln Asp Leu Ile His Arg Ser
                 110
                                     115
 Lys Met Ala Arg Cys Arg Gly Arg Phe Val Cys Pro Val Ile Leu
                 125
                                     130
Phe Lys Gly Lys His Ile Cys Arg Ser Ala Thr Leu Ala Gly Trp
                 140
                                     145
Gly Glu Leu Tyr Gly Arg Ser Gly Tyr Asn Tyr Phe Phe Ser Gly
                 155
                                     160
Gly Ala Asp Asp Ala Trp Ala Asp Val Glu Asp Val Thr Glu Glu
                 170
                                     175
Asp Cys Ala Leu Arg Ser Gly Asp Thr His Leu Phe Asp Lys Val
                 185
                                     190
Arg Gly Tyr Asp Ile Lys Leu Leu Arg Tyr Leu Ser Val Lys Tyr
                 200
                                                         210
Ile Cys Asp Leu Met Val Glu Asn Lys Lys Val Lys Phe Gly Met
                215
                                     220
Asn Val Thr Ser Ser Glu Lys Val Asp Lys Ala Gln Arg Tyr Ala
                230
                                     235
Asp Phe Thr Leu Leu Ser Ile Pro Tyr Pro Gly Cys Glu Phe Phe
                245
Lys Glu Tyr Lys Asp Arg Asp Tyr Met Ala Glu Gly Leu Ile Phe
                260
Asn Trp Lys Gln Asp Tyr Val Asp Ala Pro Leu Ser Ile Pro Asp
                275
                                     280
Phe Leu Thr His Ser Leu Asn Ile Asp Trp Ser Gln Tyr Gln Cys
                290
                                     295
Trp Asp Leu Val Gln Gln Thr Gln Asn Tyr Leu Lys Leu Leu Leu
                305
                                     310
Ser Leu Val Asn Ser Asp Asp Ser Gly Leu Leu Val His Cys
                320
                                    325
Ile Ser Gly Trp Asp Arg Thr Pro Leu Phe Ile Ser Leu Leu Arg
                335
                                    340
Leu Ser Leu Trp Ala Asp Gly Leu Ile His Thr Ser Leu Lys Pro
                350
                                    355
Thr Glu Ile Leu Tyr Leu Thr Val Ala Tyr Asp Trp Phe Leu Phe
                365
Gly His Met Leu Val Asp Arg Leu Ser Lys Gly Glu Glu Ile Phe
                380
Phe Phe Cys Phe Asn Phe Leu Lys His Ile Thr Ser Glu Glu Phe
                395
                                    400
Ser Ala Leu Lys Thr Gln Arg Arg Lys Ser Leu Pro Ala Arg Asp
Gly Gly Phe Thr Leu Glu Asp Ile Cys Met Leu Arg Arg Lys Asp
Arg Gly Ser Thr Thr Ser Leu Gly Ser Asp Phe Ser Leu Val Met
```

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440
                                    445
Glu Ser Ser Pro Gly Ala Thr Gly Ser Phe Thr Tyr Glu Ala Val
                455
                                   460
Glu Leu Val Pro Ala Gly Ala Pro Thr Gln Ala Ala Trp Leu Ala
                470
                                    475
Ala Leu Ser Asp Arg Glu Thr Arg Leu Gln Glu Val Arg Ser Ala
                485
                                    490
Phe Leu Ala Ala Tyr Ser Ser Thr Val Gly Leu Arg Ala Val Ala
                500
                                    505
Pro Ser Pro Ser Gly Ala Ile Gly Gly Leu Leu Glu Gln Phe Ala
                515
                                    520
                                                        525
Arg Gly Val Gly Leu Arg Ser Ile Ser Ser Asn Ala Leu
                530
<210> 93
<211> 58
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2831245
<400> 93
Met Glu Met Lys Gly Ser Arg Val Trp Leu Leu Leu Phe Met
                 5
                                    10
Trp Lys Ala Arg Pro Thr Phe Phe Gln Ser Cys Val Val Pro Phe
                                     25
Ile Leu Ser Pro Gln Asn Cys Val Gln Thr His Ser Leu Gly Pro
                 35
                                     40
Gly Val Trp Leu Gly Val Phe Pro Ser Gly Ser Leu His
<210> 94
<211> 119
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 3116250
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<210> 95 <211> 128 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 3129630 <400> 95 Met Ala Tyr Ser Thr Val Gln Arg Val Ala Leu Ala Ser Gly Leu Val Leu Ala Leu Ser Leu Leu Pro Lys Ala Phe Leu Ser Arg 20 30 Gly Lys Arg Gln Glu Pro Pro Pro Thr Pro Glu Gly Lys Leu Gly 35 40 45 Arg Phe Pro Pro Met Met His His His Gln Ala Pro Ser Asp Gly 50 Gln Thr Pro Gly Ala Arg Phe Gln Arg Ser His Leu Ala Glu Ala 65 Phe Ala Lys Ala Lys Gly Ser Gly Gly Gly Ala Gly Gly Gly 80 Ser Gly Arg Gly Leu Met Gly Gln Ile Ile Pro Ile Tyr Gly Phe 95 100 Gly Ile Phe Leu Tyr Ile Leu Tyr Ile Leu Phe Lys Val Ser Arg 110 Ile Ile Leu Ile Ile Leu His Gln 125

```
20
                                     25
Phe Gln Leu Ser Ala Pro His Glu Asp Ala Arg Leu Thr Pro Glu
                 35
                                     40
Glu Leu Glu Arg Ala Ser Leu Leu Gln Ile Leu Pro Glu Met Leu
                 50
                                     55
Gly Ala Glu Arg Gly Asp Ile Leu Arg Lys Ala Asp Ser Ser Thr
                 65
                                     70
Asn Ile Phe Asn Pro Arg Gly Asn Leu Arg Lys Phe Gln Asp Phe
                 80
                                     85
Ser Gly Gln Asp Pro Asn Ile Leu Leu Ser His Leu Leu Ala Arg
                 95
                                    100
Ile Trp Lys Pro Tyr Lys Lys Arg Glu Thr Pro Asp Cys Phe Trp
                                                        120
Lys Tyr Cys Val
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<210> 97
<211> 182
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1236968

<400> 97
Met Trp Pro Leu Ser Ser Asp Se

Met Trp Pro Leu Ser Ser Asp Ser Ser Trp Ser Leu Trp Ile Ser Thr Gly Met Ala Pro Ala Pro Ser Ser Ser Thr Arg Ser Phe Ser 20 Glu Ser Leu Lys Gln Lys Leu Val Arg Val Leu Glu Glu Asn Leu 35 Ile Leu Ser Glu Lys Ile Gln Gln Leu Glu Glu Gly Ala Ala Ile 50 Ser Ile Val Ser Gly Gln Gln Ser His Thr Tyr Asp Asp Leu Leu 65 70 His Lys Asn Gln Gln Leu Thr Met Gln Val Ala Cys Leu Asn Gln 80 Glu Leu Ala Gln Leu Lys Lys Leu Glu Lys Thr Val Ala Ile Leu 95 100 His Glu Ser Gln Arg Ser Leu Val Val Thr Asn Glu Tyr Leu Leu 110 115 Gln Gln Leu Asn Lys Glu Pro Lys Gly Tyr Ser Gly Lys Ala Leu 125 130 Leu Pro Pro Glu Lys Gly His His Leu Gly Arg Ser Ser Pro Phe 145 Gly Lys Ser Thr Leu Ser Ser Ser Pro Val Ala His Glu Thr 160 Gly Gln Tyr Leu Ile Gln Ser Val Leu Asp Ala Ala Pro Glu Pro 175 Gly Leu

GIY Leu

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<210> 98
 <211> 237
 <212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1334153
<400> 98
Met Lys Gly Ile Leu Val Ala Gly Ile Thr Ala Val Leu Val Ala
Ala Val Glu Ser Leu Ser Cys Val Pro Cys Asn Ser Trp Glu Lys
Ser Cys Val Asn Ser Ile Ala Ser Glu Cys Pro Ser His Ala Asn
                                     40
Thr Ser Cys Ile Ser Ser Ser Ala Ser Ser Ser Leu Glu Thr Pro
Val Arg Leu Tyr Gln Asn Met Phe Cys Ser Ala Glu Asn Cys Ser
                 65
Glu Glu Thr His Ile Thr Ala Phe Thr Val His Val Ser Ala Glu
                 80
Glu His Phe His Phe Val Ser Gln Cys Cys Gln Gly Lys Glu Cys
                 95
                                    100
Ser Asn Thr Ser Asp Ala Leu Asp Pro Pro Leu Lys Asn Val Ser
                110
                                    115
Ser Asn Ala Glu Cys Pro Ala Cys Tyr Glu Ser Asn Gly Thr Ser
                125
                                    130
Cys Arg Gly Lys Pro Trp Lys Cys Tyr Glu Glu Glu Gln Cys Val
                140
                                    145
Phe Leu Val Ala Glu Leu Lys Asn Asp Ile Glu Ser Lys Ser Leu
                155
                                    160
Val Leu Lys Gly Cys Ser Asn Val Ser Asn Ala Thr Cys Gln Phe
                170
                                   175
Leu Ser Gly Glu Asn Lys Thr Leu Gly Gly Val Ile Phe Arg Lys
                185
                                   190
Phe Glu Cys Ala Asn Val Asn Ser Leu Thr Pro Thr Ser Ala Pro
                200
                                   205
Thr Thr Ser His Asn Val Gly Ser Lys Ala Ser Leu Tyr Leu Leu
               215
                                    220
Ala Leu Ala Ser Leu Leu Leu Arg Gly Leu Leu Pro
               230
<210> 99
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<210> 99
<211> 160
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1396975
<400> 99
Met Arg Pro Gly Pro Met Leu Gln Ala Arg Val Ser Ile Pro Ala
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10
Ala Leu Gly Thr Leu Phe Pro Arg Pro Gly Trp Ala Pro Gly Glu
                                     25
Val Ser Ser Glu Ile Ser Ser Arg Asp Leu Leu Asn Pro His Pro
                                     40
Ser Thr Pro Ser Cys Cys Ser Gln Ser Trp Ser Pro Met Ser Val
                                     55
Leu Glu Pro Asp Ser Arg Gly Pro Pro Pro Ile Ser Leu Thr His
                                     70
Thr Gly Ile His Thr Pro Gln Lys Thr Ser Gln Met Arg Pro Asp
                                                         90
Ser Gly Ser Arg Gly Met Cys Phe Cys Pro Cys Lys Gly Phe Gly
                 95
Glu Gly Gly Asn Ile Val Glu Ala Gly Lys Ser Pro Gln Thr Cys
                                    115
                                                        120
Ala His Ala Pro Pro Ala Leu Arg Phe His Ser Ala Phe Ser Glu
                125
                                    130
Cys Pro Cys Cys Thr Gln Thr Thr Gly Gln Glu Arg Pro Ser Leu
                140
Pro Leu Gln Pro Leu Ser Leu Pro Phe Asn
                155
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<210> 100
<211> 148
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1501749
<400> 100
Met Ala Ala Ser Pro Ala Arg Pro Ala Val Leu Ala Leu Thr Gly
                  5
                                     10
Leu Ala Leu Leu Leu Leu Cys Trp Gly Pro Gly Gly Ile Ser
                 20
Gly Asn Lys Leu Lys Leu Met Leu Gln Lys Arg Glu Ala Pro Val
                 35
Pro Thr Lys Thr Lys Val Ala Val Asp Glu Asn Lys Ala Lys Glu
                 50
Phe Leu Gly Ser Leu Lys Arg Gln Lys Arg Gln Leu Trp Asp Arg
                 65
                                     70
Thr Arg Pro Glu Val Gln Gln Trp Tyr Gln Gln Phe Leu Tyr Met
                 80
Gly Phe Asp Glu Ala Lys Phe Glu Asp Asp Ile Thr Tyr Trp Leu
                 95
                                    100
Asn Arg Asp Arg Asn Gly His Glu Tyr Tyr Gly Asp Tyr Tyr Gln
                110
                                    115
Arg His Tyr Asp Glu Asp Ser Ala Ile Gly Pro Arg Ser Pro Tyr
                125
                                    130
Gly Phe Arg His Gly Ala Ser Val Asn Tyr Asp Asp Tyr
```

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<210> 101
<211> 170
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1575240
<400> 101
Met Thr Pro Thr Lys Arg Glu Pro Pro Ala Ala Pro Leu Leu Leu
Arg Val Leu Pro Gln Leu Ser Ala Met Ser Leu Arg Leu Ser Thr
                 20
Arg Arg Glu Asp Met Ile Gly Gln Thr Ser Gly Met Cys Ser Phe
                 35
                                     40
Cys Ser Phe Gln Asn Met Arg Gly Glu Ser Ile Trp Leu Leu Cys
                 50
                                     55
Leu Glu Glu Gly Ala Gly Leu Cys Gln Asn Ser Leu Asp Lys
                                     70
Arg Phe Ser Gln Lys Glu Gly Cys Ser Asp Asp Lys Ser Pro Leu
                 80
                                     85
His His Phe Pro Trp Leu Ser Asp Ala Pro Pro Ser Ser His Ala
                 95
                                    100
Arg Thr Ser Glu Ile Arg Leu Pro Pro Asp Ile Thr Gln Pro Cys
                                    115
Leu Thr Lys Arg Gln Trp Phe Ile Pro Ser Leu Gly Glu Lys Arg
                                    130
Gly Asn Ala Lys Leu Leu His Gln Leu Leu Ile Leu Leu Pro Ala
                140
                                    145
                                                        150
Arg Asn Pro Gly Tyr Leu Gln Val Ser Leu Pro Leu Val Trp Ser
                155
                                    160
                                                        165
Trp Leu Ser Leu Phe
                170
<210> 102
<211> 150
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 1647884
<400> 102
Met Gly Ala Ala Arp Ala Arg Pro Leu Ser Val Ser Phe Leu
Leu Leu Leu Pro Leu Pro Gly Met Pro Ala Gly Ser Trp Asp
Pro Ala Gly Tyr Leu Leu Tyr Cys Pro Cys Met Gly Lys Ala Ser
                                     40
```

Gln Ala Leu Cys Ser Asp Gly Glu Thr Glu Ala Gly Arg Gly Lys

```
Ala Thr Pro Gln Met Arg Pro Glu Thr Pro Ser Gln Val Gln Glu
                65
                                     70
Arg Thr Ser Glu Arg Asp Gly Ala Cys Ser Ser Pro Leu Cys Leu
                 80
Ser Cys Lys Gly Thr Glu Gly Pro Thr Cys Pro Thr Phe His Leu
                 95
                                    100
Thr Asp Glu Lys Thr Glu Ala Gly Arg Gly Tyr Val Thr Cys Leu
                110
                                    115
Arg Ser Lys Pro Val Gln Gly Pro Val Asn Gly Val Ser Gly Ala
                125
                                   130
Gly Leu Asp Val Thr Asp Pro Arg Trp Leu Leu Val Ile Phe His
                                   145
```

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<210> 103
<211> 142
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 1661144
<400> 103
Met Gly Cys Leu Val Trp Gly Pro Ser Trp Pro Pro Leu Ser Leu
                                     10
Leu Ala Ser Leu Leu His Ser Gly Ile Ala Gly Arg Cys Leu Leu
Cys Leu Phe Lys Gly Leu Ala Ala Ala Ala Ser Leu Gln Ile Arg
Asp Leu Ala Ser Arg Leu Thr Thr Gly Pro Arg Thr Cys Arg Val
                 50
Gln Pro Pro Pro His Pro Gln Ser Ser Pro Pro Trp Pro Gly Pro
                                     70
Pro Gly Ala Glu Thr Cys Arg Pro Leu Ser Arg Thr Val Gly Gly
                 80
                                     85
Val Cys Pro Ser Asp Trp Pro Val Ser Trp Leu Leu Pro Pro
                 95
                                    100
Leu Pro Glu Val Val Thr Cys Ser Cys Pro Arg Ile Lys Ala Arg
                110
                                    115
                                                        120
Pro Glu Arg Thr Pro Glu Leu Leu Cys Ala Trp Gly Gly Arg Gly
                125
                                    130
Lys His Ser Gln Leu Val Ala
                140
```

<210> 104 <211> 110 <212> PRT <213> Homo sapiens <220> <221> misc_feature

<223> Incyte Clone No: 1685409

Met Glu Thr Gly Arg Leu Leu Ser Leu Ser Ser Leu Pro Leu Val 10 Leu Leu Gly Trp Glu Tyr Ser Ser Gln Thr Leu Asn Leu Val Pro 20 25 Ser Thr Ser Ile Leu Ser Phe Val Pro Phe Ile Pro Leu His Leu 35 40 Val Leu Phe Ala Leu Trp Tyr Leu Pro Val Pro His His Leu Tyr 50 55 Pro Gln Gly Leu Gly Asp His Ala Ala Glu Ala Glu Lys Gly Lys 65 Arg Glu Glu Gly Gly Thr Gln Val Ala Leu Trp Leu Arg Val Gln 80 85 Pro Ser Cys Pro Ser Pro Val Cys Leu Glu Pro Val Pro Pro Arg 95 Ser Arg Phe Leu Leu 110

<210> 105 <211> 120 <212> PRT <213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 1731419

<400> 105 Met Ser Arg Ala Gly Met Leu Gly Val Val Cys Ala Leu Leu Val 10 Trp Ala Tyr Leu Ala Val Gly Lys Leu Val Val Arg Met Thr Phe 20 Thr Glu Leu Cys Thr His His Pro Trp Ser Leu Arg Cys Glu Ser 35 40 Phe Cys Arg Ser Arg Val Thr Ala Cys Leu Pro Ala Pro Ala Pro 50 55 Trp Leu Arg Pro Phe Leu Cys Pro Met Leu Phe Ser Asp Arg Asn 65 70 Pro Val Glu Cys His Leu Phe Gly Glu Ala Val Ser Asp Pro Val 80 85 Cys Lys Gly Leu Leu Pro His Tyr Phe Trp His Pro Thr Phe Phe 95 100 Pro Val Lys Ala Asn Cys Leu Val Ser Phe Cys Pro Thr Thr Val 115

<210> 106 <211> 135 <212> PRT <213> Homo sapiens

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<220>
<221> misc_feature
<223> Incyte Clone No: 2650265
Met Ala Arg Phe Trp Val Cys Val Ala Gly Ala Gly Phe Phe Leu
                                     10
Ala Phe Leu Val Leu His Ser Arg Phe Cys Gly Ser Pro Val Leu
                 20
                                     25
Arg Asn Phe Thr Phe Ala Val Ser Trp Arg Thr Glu Lys Ile Leu
                 35
                                     40
Tyr Arg Leu Asp Val Gly Trp Pro Lys His Pro Glu Tyr Phe Thr
                 50
Gly Thr Thr Phe Cys Val Ala Val Asp Ser Leu Asn Gly Leu Val
                 65
Tyr Ile Gly Gln Arg Gly Asp Asn Ile Pro Lys Ile Leu Val Phe
                 80
Thr Glu Asp Gly Tyr Phe Leu Arg Ala Trp Asn Tyr Thr Val Asp
                 95
                                    100
Thr Pro His Gly Ile Phe Ala Ala Ser Thr Leu Tyr Glu Gln Ser
                110
                                    115
Val Trp Ile Thr Asp Val Gly Ser Gly Met Tyr Ser Asn Ile Tyr
                125
<210> 107
<211> 301
<212> PRT
<213> Homo sapiens
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<220>
<221> misc feature
<223> Incyte Clone No: 2677129
Met Leu Met Ile Ile Ile Glu Pro Phe Ser Val Leu Ile Leu
Phe Lys Ser Gly Ile Leu Ala Asp Phe Phe Ala Leu Leu Leu
                 20
Ile Asn Phe Phe Leu Val Ser Phe Phe Leu Ala Tyr Pro Leu Phe
                35
Asn Asn Gln Ile Asn Ser Arg Ser Met Asn Glu Ile Lys Asn Leu
                50
Gln Tyr Leu Pro Arg Thr Ser Glu Pro Arg Glu Val Leu Phe Glu
                65
                                    70
Asp Arg Thr Arg Ala His Ala Asp His Val Gly Gln Gly Phe Asp
                80
                                    85
Trp Gln Ser Thr Ala Ala Val Gly Val Leu Lys Ala Val Gln Phe
                95
                                   100
Gly Glu Trp Ser Asp Gln Pro Arg Ile Thr Lys Asp Val Ile Cys
               110
                                   115
```

Phe His Ala Glu Asp Phe Thr Asp Val Val Gln Arg Leu Gln Leu

Asp Leu His Glu Pro Pro Val Ser Gln Cys Val Gln Trp Val Asp

125

140

130

145

Glu Ala Lys Leu Asn Gln Met Arg Arg Glu Gly Ile Arg Tyr Ala 155 160 Arg Ile Gln Leu Cys Asp Asn Asp Ile Tyr Phe Ile Pro Arg Asn 170 175 Val Ile His Gln Phe Lys Thr Val Ser Ala Val Cys Ser Leu Ala 185 190 Trp His Ile Arg Leu Lys Gln Tyr His Pro Val Val Glu Ala Thr 200 205 Gln Asn Thr Glu Ser Asn Ser Asn Met Asp Cys Gly Leu Thr Gly 215 220 Lys Arg Glu Leu Glu Val Asp Ser Gln Cys Val Arg Ile Lys Thr 230 235 Glu Ser Glu Glu Ala Cys Thr Glu Ile Gln Leu Leu Thr Thr Ala 245 250 Ser Ser Ser Phe Pro Pro Ala Ser Glu Leu Asn Leu Gln Gln Asp 260 265 Gln Lys Thr Gln Pro Ile Pro Val Leu Lys Val Glu Ser Arg Leu 275 280 Asp Ser Asp Gln Gln His Asn Leu Gln Glu His Ser Thr Thr Ser 290 295 Val

<210> 108 <211> 103 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 3151073 <400> 108 Met Ser Phe Val Pro Gly Leu Leu Cys Phe Val Leu Leu Leu 1 5 Cys Val Ser Pro Val Tyr Leu Pro Ser Arg Ser Pro Ser Thr Phe 20 25 Pro Ile Ser Glu Pro Leu Ser Phe Ile Gly Met Ser Ala Trp Pro 35 40 Gln Cys Ser Pro Ile Tyr Ser Gln Thr Pro Gly Leu Ala Tyr Glu 50 Pro Ser Ser Phe Pro Lys Arg Arg Tyr Trp Val Cys Thr Leu His 70 Glu Ile Lys Trp Glu Cys Pro Arg Ser Arg Arg Thr Ser Asp Ala 85 Val His Ala Asn Lys Leu Gly Leu Pro Leu Lys Ile Ile

<210> 109 <211> 95 <212> PRT <213> Homo sapiens

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<220>
<221> misc feature
<223> Incyte Clone No: 3170095
Met Lys Phe Leu Leu Val Leu Ala Ala Leu Gly Phe Leu Thr
                                     10
Gln Val Ile Pro Ala Ser Ala Gly Gly Ser Lys Cys Val Ser Asn
                 20
Thr Pro Gly Tyr Cys Arg Thr Cys Cys His Trp Gly Glu Thr Ala
                 35
Leu Phe Met Cys Asn Ala Ser Arg Lys Cys Cys Ile Ser Tyr Ser
                 50
Phe Leu Pro Lys Pro Asp Leu Pro Gln Leu Ile Gly Asn His Trp
Gln Ser Arg Arg Arg Asn Thr Gln Arg Lys Asp Lys Lys Gln Gln
                 80
Thr Thr Val Thr Ser
<210> 110
<211> 113
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 3475168
<400> 110
Met Ser Pro Ser Pro Arg Trp Gly Phe Leu Cys Val Leu Phe Thr
                 5
                                     10
Ala Val His Pro Ala Pro Ser Thr Ala Pro Val Gln Asp Lys Cys
Pro Val Asn Thr Trp Glu Ala Met Gln Ala Ser Ser Gln Gln Leu
                 35
Leu Gln Thr Asp Pro Arg Pro Lys Pro Phe Leu Leu Pro Pro Leu
                                     55
Pro Pro Leu Leu Leu Ile Ser Ala Gly Thr Glu Val Ser Ser Leu
                                     70
                                                         75
Val Phe Gln Lys Ser Pro Leu His Thr Gln Pro Glu Gly Ala Ile
                                     85
Lys Thr Ala Gly Gln Pro Thr Ser Val His Ser Lys Val Leu Ser
                95
                                    100
Lys Gly Ser Leu Leu Leu Gly Glu
                110
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<210> 111 <211> 234 <212> PRT <213> Homo sapiens

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<220>
<221> misc_feature
<223> Incyte Clone No: 3836893
<400> 111
Met Arg Lys Thr Arg Leu Trp Gly Leu Leu Trp Met Leu Phe Val
                                      10
Ser Glu Leu Arg Ala Ala Thr Lys Leu Thr Glu Glu Lys Tyr Glu
Leu Lys Glu Gly Gln Thr Leu Asp Val Lys Cys Asp Tyr Thr Leu
                 35
Glu Lys Phe Ala Ser Ser Gln Lys Ala Trp Gln Ile Ile Arg Asp
                                                          60
Gly Glu Met Pro Lys Thr Leu Ala Cys Thr Glu Arg Pro Ser Lys
                 65
                                      70
Asn Ser His Pro Val Gln Val Gly Arg Ile Ile Leu Glu Asp Tyr
                                                          90
His Asp His Gly Leu Leu Arg Val Arg Met Val Asn Leu Gln Val
                 95
                                    100
Glu Asp Ser Gly Leu Tyr Gln Cys Val Ile Tyr Gln Pro Pro Lys
                                    115
                                                         120
Glu Pro His Met Leu Phe Asp Arg Ile Arg Leu Val Val Thr Lys
                                    130
                                                         135
Gly Phe Ser Gly Thr Pro Gly Ser Asn Glu Asn Ser Thr Gln Asn
                                    145
Val Tyr Lys Ile Pro Pro Thr Thr Lys Ala Leu Cys Pro Leu
                155
                                    160
Tyr Thr Ser Pro Arg Thr Val Thr Gln Ala Pro Pro Lys Ser Thr
                170
Ala Asp Val Ser Thr Pro Asp Ser Glu Ile Asn Leu Thr Asn Val
                185
Thr Asp Ile Ile Arg Val Pro Val Phe Asn Ile Val Ile Leu Leu
                                    205
Ala Gly Gly Phe Leu Ser Lys Ser Leu Val Phe Ser Val Leu Phe
                215
Ala Val Thr Leu Arg Ser Phe Val Pro
                230
<210> 112
<211> 119
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      Ser Arg Gly Asn Gly Lys Met Thr
      Ser Pro Pro Arg Gly Pro Gly 60

      Thr His Arg Thr Ala Glu Leu Ala Arg Ala Glu Glu Leu Leu Glu 65
      70

      Gln Gln Leu Glu Leu Tyr Gln Ala Leu Leu Glu 65
      85

      80
      85

      81
      90

      Ala Trp Glu Ala Gln Ala Leu Val Leu Lys 100
      100

      Glu Gln Met Arg Arg His Gln Glu Ser Leu Gly Gly Gly Ala
      115
```

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<210> 113
<211> 200
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 1003916
<400> 113
Met Ala Ser Ser Leu Thr Cys Thr Gly Val Ile Trp Ala Leu Leu
 1
                                     10
Ser Phe Leu Cys Ala Ala Thr Ser Cys Val Gly Phe Phe Met Pro
                                     25
Tyr Trp Leu Trp Gly Ser Gln Leu Gly Lys Pro Val Ser Phe Gly
                                     40
Thr Phe Arg Arg Cys Ser Tyr Pro Val His Asp Glu Ser Arg Gln
                 50
                                     55
Met Met Val Met Val Glu Glu Cys Gly Arg Tyr Ala Ser Phe Gln
                                     70
Gly Ile Pro Ser Ala Glu Trp Arg Ile Cys Thr Ile Val Thr Gly
                 80
                                     85
                                                         90
Leu Gly Cys Gly Leu Leu Leu Val Ala Leu Thr Ala Leu Met
                 95
                                    100
                                                        105
Gly Cys Cys Val Ser Asp Leu Ile Ser Arg Thr Val Gly Arg Val
                110
                                    115
                                                        120
Ala Gly Gly Ile Gln Phe Leu Gly Gly Leu Leu Ile Gly Ala Gly
                                    130
                                                        135
Cys Ala Leu Tyr Pro Leu Gly Trp Asp Ser Glu Glu Val Arg Gln
                140
                                    145
                                                        150
Thr Cys Gly Tyr Thr Ser Gly Gln Phe Asp Leu Gly Lys Cys Glu
                                    160
Ile Gly Trp Ala Tyr Tyr Cys Thr Gly Ala Gly Ala Thr Ala Ala
                170
                                    175
Met Leu Leu Cys Thr Trp Leu Ala Cys Phe Ser Gly Lys Lys Gln
                                    190
Lys His Tyr Pro Tyr
              200
```

<210> 114

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<211> 225
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte Clone No: 2093492
 <400> 114
 Met Gly Phe Arg Leu Glu Gly Ile Phe Pro Ala Ala Leu Leu Pro
                                      10
 Leu Leu Leu Thr Met Ile Leu Phe Leu Gly Pro Leu Met Gln Leu
 Ser Met Asp Cys Pro Cys Asp Leu Ala Asp Gly Leu Lys Val Val
                                     40
 Leu Ala Pro Arg Ser Trp Ala Arg Cys Leu Thr Asp Met Arg Trp
 Leu Arg Asn Gln Val Ile Ala Pro Leu Thr Glu Glu Leu Val Phe
 Arg Ala Cys Met Leu Pro Met Leu Ala Pro Cys Met Gly Leu Gly
                                     85
 Pro Ala Val Phe Thr Cys Pro Leu Phe Phe Gly Val Ala His Phe
                  95
His His Ile Ile Glu Gln Leu Arg Phe Arg Gln Ser Ser Val Gly
Asn Ile Phe Leu Ser Ala Ala Phe Gln Phe Ser Tyr Thr Ala Val
                125
Phe Gly Ala Tyr Thr Ala Phe Leu Phe Ile Arg Thr Gly His Leu
Ile Gly Pro Val Leu Cys His Ser Phe Cys Asn Tyr Met Gly Phe
                                    160
Pro Ala Val Cys Ala Ala Leu Glu His Pro Gln Arg Arg Pro Leu
                170
                                    175
Leu Ala Gly Tyr Ala Leu Gly Val Gly Leu Phe Leu Leu Leu
                185
                                    190
Gln Pro Leu Thr Asp Pro Lys Leu Tyr Gly Ser Leu Pro Leu Cys
                200
                                    205
Val Leu Leu Glu Arg Ala Gly Asp Ser Glu Ala Pro Leu Cys Ser
                215
                                    220
<210> 115
<211> 155
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2108789
<400> 115
Met Ser Gly Leu Leu Ile Pro Pro Leu Pro Gly Trp Val Leu Gly
```

10

Pro Leu Met Trp Ala Cys Arg Pro Pro Gln Asp Glu Pro Ser Gly

5

```
Thr Asp Pro Pro Pro Pro Arg Leu Gln Pro His His Val Ser Gly
                 35
Leu Gly Leu Gly Gln Ala Trp Ala Gln Ser Trp Ala Pro Arg Gly
Ser Pro Pro Leu Thr Trp Leu Leu Pro Thr Leu Pro Leu Lys Asp
                 65
Gly Pro Ala Ala Arg Leu Pro Pro Pro Pro His Thr Leu Gly
                 80
                                     85
                                                         90
Gly Leu Ser His Pro Pro Gln Pro Arg Ser Ala Gln Thr Asp Pro
                 95
                                    100
His Ser Ile Pro Arg Pro Ala Ala Gln Val Arg Gly Pro Val Leu
                110
                                    115
Pro Gly Ala Trp Ala Thr Pro Tyr Ala Ile Ser Ser Glu Gln Pro
                125
                                   130
Gly Pro Thr Asp Pro His Ala Leu Ser Tyr Val Pro Phe Ser Pro
                                   145
Asp Phe Phe Cys Thr
                155
```

<210> 116

<211> 468 <212> PRT <213> Homo sapiens <220> <221> misc feature <223> Incyte Clone No: 2171401 <400> 116 Met Gly Arg Gly Trp Gly Phe Leu Phe Gly Leu Leu Gly Ala Val Trp Leu Leu Ser Ser Gly His Gly Glu Glu Gln Pro Pro Glu Thr Ala Ala Gln Arg Cys Phe Cys Gln Val Ser Gly Tyr Leu Asp Asp 35 Cys Thr Cys Asp Val Glu Thr Ile Asp Arg Phe Asn Asn Tyr Arg 50 Leu Phe Pro Arg Leu Gln Lys Leu Leu Glu Ser Asp Tyr Phe Arg Tyr Tyr Lys Val Asn Leu Lys Arg Pro Cys Pro Phe Trp Asn Asp Ile Ser Gln Cys Gly Arg Arg Asp Cys Ala Val Lys Pro Cys Gln 105 Ser Asp Glu Val Pro Asp Gly Ile Lys Ser Ala Ser Tyr Lys Tyr 110 120 Ser Glu Glu Ala Asn Asn Leu Ile Glu Glu Cys Glu Gln Ala Glu 125 Arg Leu Gly Ala Val Asp Glu Ser Leu Ser Glu Glu Thr Gln Lys 140 Ala Val Leu Gln Trp Thr Lys His Asp Asp Ser Ser Asp Asn Phe 155 160 Cys Glu Ala Asp Asp Ile Gln Ser Pro Glu Ala Glu Tyr Val Asp 175 Leu Leu Leu Asn Pro Glu Arg Tyr Thr Gly Tyr Lys Gly Pro Asp

```
190
                185
Ala Trp Lys Ile Trp Asn Val Ile Tyr Glu Glu Asn Cys Phe Lys
                200
                                   205
Pro Gln Thr Ile Lys Arg Pro Leu Asn Pro Leu Ala Ser Gly Gln
                215
                                   220
Gly Thr Ser Glu Glu Asn Thr Phe Tyr Ser Trp Leu Glu Gly Leu
               230
                                   235
Cys Val Glu Lys Arg Ala Phe Tyr Arg Leu Ile Ser Gly Leu His
               245
                                   250
Ala Ser Ile Asn Val His Leu Ser Ala Arg Tyr Leu Leu Gln Glu
               260
                                   265
Thr Trp Leu Glu Lys Lys Trp Gly His Asn Ile Thr Glu Phe Gln
                275
                                   280
Gln Arg Phe Asp Gly Ile Leu Thr Glu Gly Glu Gly Pro Arg Arg
               290
                                   295
Leu Lys Asn Leu Tyr Phe Leu Tyr Leu Ile Glu Leu Arg Ala Leu
               305
                                   310
Ser Lys Val Leu Pro Phe Phe Glu Arg Pro Asp Phe Gln Leu Phe
               320
                                    325
Thr Gly Asn Lys Ile Gln Asp Glu Glu Asn Lys Met Leu Leu Leu
                335
                                    340
Glu Ile Leu His Glu Ile Lys Ser Phe Pro Leu His Phe Asp Glu
                350
                                    355
Asn Ser Phe Phe Ala Gly Asp Lys Lys Glu Ala His Lys Leu Lys
               365
                                   370
Glu Asp Phe Arg Leu His Phe Arg Asn Ile Ser Arg Ile Met Asp
                380
                                   385
Cys Val Gly Cys Phe Lys Cys Arg Leu Trp Gly Lys Leu Gln Thr
                395
                                   400
Gln Gly Leu Gly Thr Ala Leu Lys Ile Leu Phe Ser Glu Lys Leu
                410
                                   415
Ile Ala Asn Met Pro Glu Ser Gly Pro Ser Tyr Glu Phe His Leu
                425
                                   430
Thr Arg Gln Glu Ile Val Ser Leu Phe Asn Ala Phe Gly Arg Ile
                440
                                   445
Ser Thr Ser Val Lys Glu Leu Glu Asn Phe Arg Asn Leu Leu Gln
               455
Asn Ile His
```

```
<210> 117
<211> 403
<212> PRT
<213> Homo sapiens
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<220>

<221> misc_feature

<223> Incyte Clone No: 2212530

<400> 117

 Met
 Ser
 Thr
 Ser
 Pro
 Ala
 Ala
 Met
 Leu
 Leu
 Arg
 Arg
 Leu

 1
 5
 5
 10
 15

 Arg
 Arg
 Leu
 Ser
 Thr
 Ala
 Val
 Gln
 Leu
 Phe
 Ile
 Leu

 20
 25
 30

 Thr
 Val
 Val
 Thr
 Phe
 Gly
 Leu
 Leu
 Ala
 Pro
 Leu
 Ala
 Cys
 His
 Arg

```
35
                                     40
Leu Leu His Ser Tyr Phe Tyr Leu Arg His Trp His Leu Asn Gln
                 50
Met Ser Gln Glu Phe Leu Gln Gln Ser Leu Lys Glu Gly Glu Ala
                 65
Ala Leu His Tyr Phe Glu Glu Leu Pro Ser Ala Asn Gly Ser Val
                 80
                                     85
Pro Ile Val Trp Gln Ala Thr Pro Arg Pro Trp Leu Val Ile Thr
                 95
                                    100
Ile Ile Thr Val Asp Arg Gln Pro Gly Phe His Tyr Val Leu Gln
                110
                                    115
Val Val Ser Gln Phe His Arg Leu Leu Gln Gln Cys Gly Pro Gln
                125
                                    130
Cys Glu Gly His Gln Leu Phe Leu Cys Asn Val Glu Arg Ser Val
                140
                                    145
Ser His Phe Asp Ala Lys Leu Leu Ser Lys Tyr Val Pro Val Ala
                155
                                    160
Asn Arg Tyr Glu Gly Thr Glu Asp Asp Tyr Gly Asp Asp Pro Ser
                170
                                    175
Thr Asn Ser Phe Glu Lys Glu Lys Gln Asp Tyr Val Tyr Cys Leu
                185
                                    190
Glu Ser Ser Leu Gln Thr Tyr Asn Pro Asp Tyr Val Leu Met Val
                200
                                    205
Glu Asp Asp Ala Val Pro Glu Glu Gln Ile Phe Pro Val Leu Glu
                215
                                    220
His Leu Leu Arg Ala Arg Phe Ser Glu Pro His Leu Arg Asp Ala
                230
                                    235
Leu Tyr Leu Lys Leu Tyr His Pro Glu Arg Leu Gln His Tyr Ile
                245
                                    250
Asn Pro Glu Pro Met Arg Ile Leu Glu Trp Val Gly Val Gly Met
                260
                                    265
Leu Leu Gly Pro Leu Leu Thr Trp Ile Tyr Met Arg Phe Ala Ser
                275
                                    280
Arg Pro Gly Phe Ser Trp Pro Val Met Leu Phe Phe Ser Leu Tyr
                290
                                    295
Ser Met Gly Leu Val Glu Leu Val Gly Arg His Tyr Phe Leu Glu
                305
                                    310
Leu Arg Arg Leu Ser Pro Ser Leu Tyr Ser Val Val Pro Ala Ser
                320
                                    325
Gln Cys Cys Thr Pro Ala Met Leu Phe Pro Ala Pro Ala Ala Arg
                335
                                    340
Arg Thr Leu Thr Tyr Leu Ser Gln Val Tyr Cys His Lys Gly Phe
                350
Gly Lys Asp Met Ala Leu Tyr Ser Leu Leu Arg Ala Lys Gly Glu
                365
                                    370
Arg Ala Tyr Val Val Glu Pro Asn Leu Val Lys His Ile Gly Leu
                380
                                    385
Phe Ser Ser Leu Arg Tyr Asn Phe His Pro Ser Leu Leu
                395
```

<210> 118 <211> 131

<212> PRT

<213> Homo sapiens

```
<220>
<221> misc_feature
<223> Incyte Clone No: 2253036
<400> 118
Met Glu Arg Cys Phe His Cys Phe Pro Val His Leu Val Phe Asn
                                    10
Leu Val Gln Ser Phe Ser Pro Ile Ser Gly Val Glu Ser Cys Leu
                 20
                                    25
Leu Pro Gln Cys Asp Lys Cys Trp Pro Met Val Tyr Arg Ser Cys
                 35
                                    40
Asp Ala Ser Arg Gly Leu Val Asn Ala Cys Ile Leu Gly Phe Val
                 50
                                    55
Leu Leu Glu Cys Ser Phe Val Gly Ala Leu Asn Asn Tyr Val Arg
                65
                                    70
Ser Leu Ala Thr Leu Leu Glu Arg Thr His Gly Gly Lys Arg Leu
                 80
                                    85
Lys Leu Cys Glu Glu Ser Gln Ala Ser His Pro Ser Phe Ser Ala
                95
                                  100
Glu Pro Arg His Gln Pro Thr Cys Gln Leu Asn Ala Thr Val Arg
               110
                                   115
Val Ile Thr Ser Lys Ile Thr Arg Lys Thr Thr
               125
<210> 119
```

```
<212> PRT
<213> Homo sapiens
<220>
<221> misc_feature
<223> Incyte Clone No: 2280161
<400> 119
Met Ala Ala Ala Trp Leu Gln Val Leu Pro Val Ile Leu Leu
                                    10
Leu Leu Gly Ala His Pro Ser Pro Leu Ser Phe Phe Ser Ala Gly
                20
                                    25
Pro Ala Thr Val Ala Ala Ala Asp Arg Ser Lys Trp His Ile Pro
                35
                                     40
Ile Pro Ser Gly Lys Asn Tyr Phe Ser Phe Gly Lys Ile Leu Phe
                50
Arg Asn Thr Thr Ile Phe Leu Lys Phe Asp Gly Glu Pro Cys Asp
                65
                                    70
Leu Ser Leu Asn Ile Thr Trp Tyr Leu Lys Ser Ala Asp Cys Tyr
                80
                                    85
Asn Glu Ile Tyr Asn Phe Lys Ala Glu Glu Val Glu Leu Tyr Leu
                95
                                   100
Glu Lys Leu Lys Glu Lys Arg Gly Leu Ser Gly Lys Tyr Gln Thr
               110
                                   115
Ser Ser Lys Leu Phe Gln Asn Cys Ser Glu Leu Phe Lys Thr Gln
               125
                                   130
Thr Phe Ser Gly Asp Phe Met His Arg Leu Pro Leu Leu Gly Glu
```

140

<211> 556

145

```
Lys Gln Glu Ala Lys Glu Asn Gly Thr Asn Leu Thr Phe Ile Gly
                 155
                                     160
 Asp Lys Thr Ala Met His Glu Pro Leu Gln Thr Trp Gln Asp Ala
                 170
                                     175
 Pro Tyr Ile Phe Ile Val His Ile Gly Ile Ser Ser Lys Glu
                 185
                                     190
 Ser Ser Lys Glu Asn Ser Leu Ser Asn Leu Phe Thr Met Thr Val
                 200
                                     205
 Glu Val Lys Gly Pro Tyr Glu Tyr Leu Thr Leu Glu Asp Tyr Pro
                                     220
 Leu Met Ile Phe Phe Met Val Met Cys Ile Val Tyr Val Leu Phe
Gly Val Leu Trp Leu Ala Trp Ser Ala Cys Tyr Trp Arg Asp Leu
                 245
Leu Arg Ile Gln Phe Trp Ile Gly Ala Val Ile Phe Leu Gly Met
                 260
Leu Glu Lys Ala Val Phe Tyr Ala Glu Phe Gln Asn Ile Arg Tyr
                 275
Lys Gly Glu Ser Val Gln Gly Ala Leu Ile Leu Ala Glu Leu Leu
                290
Ser Ala Val Lys Arg Ser Leu Ala Arg Thr Leu Val Ile Ile Val
                305
Ser Leu Gly Tyr Gly Ile Val Lys Pro Arg Leu Gly Val Thr Leu
                320
His Lys Val Val Val Ala Gly Ala Leu Tyr Leu Leu Phe Ser Gly
                335
Met Glu Gly Val Leu Arg Val Thr Gly Tyr Phe Ser Tyr Pro Leu
Thr Leu Ile Val Asn Leu Ala Leu Ser Ala Val Asp Ala Cys Val
                365
Ile Leu Trp Ile Phe Ile Ser Leu Thr Gln Thr Met Lys Leu Leu
                380
Lys Leu Arg Arg Asn Ile Val Lys Leu Ser Leu Tyr Arg His Phe
                395
Thr Asn Thr Leu Ile Leu Ala Val Ala Ala Ser Ile Val Phe Ile
                410
Ile Trp Thr Thr Met Lys Phe Arg Ile Val Thr Cys Gln Ser Asp
                                    430
Trp Arg Glu Leu Trp Val Asp Asp Ala Ile Trp Arg Leu Leu Phe
                440
Ser Met Ile Leu Phe Val Ile Met Val Leu Trp Arg Pro Ser Ala
                455
                                    460
Asn Asn Gln Arg Phe Ala Phe Ser Pro Leu Ser Glu Glu Glu Glu
                                    475
Glu Asp Glu Gln Lys Glu Pro Met Leu Lys Glu Ser Phe Glu Gly
                                    490
Met Lys Met Arg Ser Thr Lys Gln Glu Pro Asn Gly Asn Ser Lys
Val Asn Lys Ala Gln Glu Asp Asp Leu Lys Trp Val Glu Glu Asn
                515
Val Pro Ser Ser Val Thr Asp Val Ala Leu Pro Ala Leu Leu Asp
                530
Ser Asp Glu Glu Arg Met Ile Thr His Phe Glu Arg Ser Lys Met
Glu
```

```
<210> 120
 <211> 514
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc feature
 <223> Incyte Clone No: 2287485
 <400> 120
 Met Ser Trp Pro Arg Arg Leu Leu Arg Tyr Leu Phe Pro Ala
                                      10
 Leu Leu His Gly Leu Gly Glu Gly Ser Ala Leu Leu His Pro
                  20
 Asp Ser Arg Ser His Pro Arg Ser Leu Glu Lys Ser Ala Trp Arg
                  35
Ala Phe Lys Glu Ser Gln Cys His His Met Leu Lys His Leu His
                  50
Asn Gly Ala Arg Ile Thr Val Gln Met Pro Pro Thr Ile Glu Gly
                  65
His Trp Val Ser Thr Gly Cys Glu Val Arg Ser Gly Pro Glu Phe
                  80
Ile Thr Arg Ser Tyr Arg Phe Tyr His Asn Asn Thr Phe Lys Ala
                  95
                                    100
Tyr Gln Phe Tyr Tyr Gly Ser Asn Arg Cys Thr Asn Pro Thr Tyr
                110
                                    115
Thr Leu Ile Ile Arg Gly Lys Ile Arg Leu Arg Gln Ala Ser Trp
                125
                                    130
Ile Ile Arg Gly Gly Thr Glu Ala Asp Tyr Gln Leu His Asn Val
                140
                                    145
Gln Val Ile Cys His Thr Glu Ala Val Ala Glu Lys Leu Gly Gln
                155
                                    160
Gln Val Asn Arg Thr Cys Pro Gly Phe Leu Ala Asp Gly Gly Pro
                170
                                    175
Trp Val Gln Asp Val Ala Tyr Asp Leu Trp Arg Glu Glu Asn Gly
                185
                                    190
Cys Glu Cys Thr Lys Ala Val Asn Phe Ala Met His Glu Leu Gln
                200
                                    205
Leu Ile Arg Val Glu Lys Gln Tyr Leu His His Asn Leu Asp His
                215
                                    220
Leu Val Glu Glu Leu Phe Leu Gly Asp Ile His Thr Asp Ala Thr
                230
                                    235
Gln Arg Met Phe Tyr Arg Pro Ser Ser Tyr Gln Pro Pro Leu Gln
                245
                                    250
Asn Ala Lys Asn His Asp His Ala Cys Ile Ala Cys Arg Ile Ile
                260
                                    265
Tyr Arg Ser Asp Glu His His Pro Pro Ile Leu Pro Pro Lys Ala
                275
                                    280
Asp Leu Thr Ile Gly Leu His Gly Glu Trp Val Ser Gln Arg Cys
                290
                                    295
Glu Val Arg Pro Glu Val Leu Phe Leu Thr Arg His Phe Ile Phe
                305
                                    310
His Asp Asn Asn Thr Trp Glu Gly His Tyr Tyr His Tyr Ser
               320
                                   325
Asp Pro Val Cys Lys His Pro Thr Phe Ser Ile Tyr Ala Arg Gly
               335
                                   340
```

```
Arg Tyr Ser Arg Gly Val Leu Ser Ser Arg Val Met Gly Gly Thr
                                    355
Glu Phe Val Phe Lys Val Asn His Met Lys Val Thr Pro Met Asp
                365
                                    370
                                                        375
Ala Ala Thr Ala Ser Leu Leu Asn Val Phe Asn Gly Asn Glu Cys
                380
                                                        390
Gly Ala Glu Gly Ser Trp Gln Val Gly Ile Gln Gln Asp Val Thr
                395
                                    400
                                                        405
His Thr Asn Gly Cys Val Ala Leu Gly Ile Lys Leu Pro His Thr
                410
                                                        420
Glu Tyr Glu Ile Phe Lys Met Glu Gln Asp Ala Arg Gly Arg Tyr
                                                        435
Leu Leu Phe Asn Gly Gln Arg Pro Ser Asp Gly Ser Ser Pro Asp
                                                        450
Arg Pro Glu Lys Arg Ala Thr Ser Tyr Gln Met Pro Leu Val Gln
Cys Ala Ser Ser Pro Arg Ala Glu Asp Leu Ala Glu Asp Ser
                470
                                    475
Gly Ser Ser Leu Tyr Gly Arg Ala Pro Gly Arg His Thr Trp Ser
                                    490
Leu Leu Ala Ala Leu Ala Cys Leu Val Pro Leu Leu His Trp
                                    505
Asn Ile Arg Arg
```

```
<210> 121
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone No: 2380344

<400> 121
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Met Leu Trp Trp Leu Val Leu Leu Leu Pro Thr Leu Lys Ser 5 10 Val Phe Cys Ser Leu Val Thr Ser Leu Tyr Leu Pro Asn Thr Glu Asp Leu Ser Leu Trp Leu Trp Pro Lys Pro Asp Leu His Ser Gly 35 40 45 Thr Arg Thr Glu Val Ser Thr His Thr Val Pro Ser Lys Pro Gly 50 55 60 Thr Ala Ser Pro Cys Trp Pro Leu Ala Gly Ala Val Pro Ser Pro 65 Thr Val Ser Arg Leu Glu Ala Leu Thr Arg Ala Val Gln Val Ala 80 85 Glu Pro Leu Gly Ser Cys Gly Phe Gln Gly Gly Pro Cys Pro Gly Arg Arg Arg Asp

<210> 122

```
<211> 431
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <223> Incyte Clone No: 2383171
 <400> 122
Met Ser Trp Val Gln Ala Thr Leu Leu Ala Arg Gly Leu Cys Arg
  1
Ala Trp Gly Gly Thr Cys Gly Ala Ala Leu Thr Gly Thr Ser Ile
                                      25
Ser Gln Val Pro Arg Arg Leu Pro Arg Gly Leu His Cys Ser Ala
                                     40
Ala Ala His Ser Ser Glu Gln Ser Leu Val Pro Ser Pro Pro Glu
                                     55
Pro Arg Gln Arg Pro Thr Lys Ala Leu Val Pro Phe Glu Asp Leu
                                      70
Phe Gly Gln Ala Pro Gly Gly Glu Arg Asp Lys Ala Ser Phe Leu
                                      85
Gln Thr Val Gln Lys Phe Ala Glu His Ser Val Arg Lys Arg Gly
                                     100
His Ile Asp Phe Ile Tyr Leu Ala Leu Arg Lys Met Arg Glu Tyr
                 110
                                     115
Gly Val Glu Arg Asp Leu Ala Val Tyr Asn Gln Leu Leu Asn Ile
                 125
                                     130
Phe Pro Lys Glu Val Phe Arg Pro Arg Asn Ile Ile Gln Arg Ile
                                     145
Phe Val His Tyr Pro Arg Gln Gln Glu Cys Gly Ile Ala Val Leu
                                     160
Glu Gln Met Glu Asn His Gly Val Met Pro Asn Lys Glu Thr Glu
                                    175
Phe Leu Leu Ile Gln Ile Phe Gly Arg Lys Ser Tyr Pro Met Leu
                                    190
Lys Leu Val Arg Leu Lys Leu Trp Phe Pro Arg Phe Met Asn Val
                                    205
Asn Pro Phe Pro Val Pro Arg Asp Leu Pro Gln Asp Pro Val Glu
                                    220
Leu Ala Met Phe Gly Leu Arg His Met Glu Pro Asp Leu Ser Ala
                                    235
Arg Val Thr Ile Tyr Gln Val Pro Leu Pro Lys Asp Ser Thr Gly
                                    250
Ala Ala Asp Pro Pro Gln Pro His Ile Val Gly Ile Gln Ser Pro
                                    265
Asp Gln Gln Ala Ala Leu Ala Arg His Asn Pro Ala Arg Pro Val
                                    280
Phe Val Glu Gly Pro Phe Ser Leu Trp Leu Arg Asn Lys Cys Val
                                    295
Tyr Tyr His Ile Leu Arg Ala Asp Leu Leu Pro Pro Glu Glu Arg
                                    310
Glu Val Glu Glu Thr Pro Glu Glu Trp Asn Leu Tyr Tyr Pro Met
                                    325
Gln Leu Asp Leu Glu Tyr Val Arg Ser Gly Trp Asp Asn Tyr Glu
                335
                                    340
                                                        345
Phe Asp Ile Asn Glu Val Glu Glu Gly Pro Val Phe Ala Met Cys
                                    355
                                                        360
```

```
      Met
      Ala
      Gly
      Ala
      His
      Asp
      Gln
      Ala
      Thr
      Met
      Ala
      Lys
      Trp
      Ile
      Gln
      375

      Gly
      Leu
      Gln
      Glu
      Thr
      Asp
      Pro
      Thr
      Leu
      Ala
      Gln
      Ile
      Pro
      Val
      Val

      Asp
      Arg
      Leu
      Ala
      Gly
      Ser
      Thr
      Arg
      Glu
      Leu
      Gln
      Thr
      Ser
      Ala

      Asp
      Leu
      Glu
      Glu
      Pro
      Leu
      Pro
      Glu
      Asp
      His
      Gln
      Glu
      Glu
      Asp

      Asp
      Asn
      Leu
      Gln
      Arg
      Gln
      Gln
      Gln
      Gln
      Gln
      Ser
      Inc
      I
```

```
<210> 123
<211> 142
<212> PRT
<213> Homo sapiens
<220>
<221> misc feature
<223> Incyte Clone No: 2396046
<400> 123
Met Leu Leu Gly Val Arg Ala Val Pro Leu Cys Ser Ala Trp Gln
Gly Ala Val Gly Leu Val Ser Leu Ala Ile Ser Ile Cys Lys His
Gly Leu Ser Ser Gln Gln Asn Leu Val Pro Gly Lys Ser Asn Val
Pro Lys Ala Ser Asp Met Pro Arg Cys Pro Pro Val Phe Gln Ser
Pro Asn Leu Thr Pro Phe Pro His His Thr Lys His Thr Ser Gln
                 65
                                                         75
Gly Ser His Leu Gly Val Pro Pro Pro Ala Pro Met Pro Trp Cys
Pro Gln Ala Gln Gly Phe Gly Leu Ser Cys Gln Ser Leu Asp Ala
                                    100
Phe Glu Gly Gln Leu Gly Cys Gly Trp Gly Val Gln Ala Ala Gly
                                    115
Glu Pro Arg Leu Arg Ile Ile His Thr Leu Leu Phe Gly Ala Phe
                                   130
Val Glu Val Ser Arg Ile Pro
```

```
<210> 124

<211> 643

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone No: 2456587
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```
<400> 124
Met Glu Cys Cys Arg Arg Ala Thr Pro Gly Thr Leu Leu Leu Phe
Leu Ala Phe Leu Leu Ser Ser Arg Thr Ala Arg Ser Glu Glu
Asp Arg Asp Gly Leu Trp Asp Ala Trp Gly Pro Trp Ser Glu Cys
Ser Arg Thr Cys Gly Gly Gly Ala Ser Tyr Ser Leu Arg Arg Cys
Leu Ser Ser Lys Ser Cys Glu Gly Arg Asn Ile Arg Tyr Arg Thr
Cys Ser Asn Val Asp Cys Pro Pro Glu Ala Gly Asp Phe Arg Ala
Gln Gln Cys Ser Ala His Asn Asp Val Lys His His Gly Gln Phe
                                   100
Tyr Glu Trp Leu Pro Val Ser Asn Asp Pro Asp Asn Pro Cys Ser
                                    115
Leu Lys Cys Gln Ala Lys Gly Thr Thr Leu Val Val Glu Leu Ala
                                    130
Pro Lys Val Leu Asp Gly Thr Arg Cys Tyr Thr Glu Ser Leu Asp
                                    145
Met Cys Ile Ser Gly Leu Cys Gln Ile Val Gly Cys Asp His Gln
                                    160
Leu Gly Ser Thr Val Lys Glu Asp Asn Cys Gly Val Cys Asn Gly
                                    175
Asp Gly Ser Thr Cys Arg Leu Val Arg Gly Gln Tyr Lys Ser Gln
                                    190
Leu Ser Ala Thr Lys Ser Asp Asp Thr Val Val Ala Ile Pro Tyr
                200
                                    205
Gly Ser Arg His Ile Arg Leu Val Leu Lys Gly Pro Asp His Leu
                                    220
Tyr Leu Glu Thr Lys Thr Leu Gln Gly Thr Lys Gly Glu Asn Ser
                230
Leu Ser Ser Thr Gly Thr Phe Leu Val Asp Asn Ser Ser Val Asp
Phe Gln Lys Phe Pro Asp Lys Glu Ile Leu Arg Met Ala Gly Pro
Leu Thr Ala Asp Phe Ile Val Lys Ile Arg Asn Ser Gly Ser Ala
                275
Asp Ser Thr Val Gln Phe Ile Phe Tyr Gln Pro Ile Ile His Arg
Trp Arg Glu Thr Asp Phe Phe Pro Cys Ser Ala Thr Cys Gly Gly
                                    310
Gly Tyr Gln Leu Thr Ser Ala Glu Cys Tyr Asp Leu Arg Ser Asn
Arg Val Val Ala Asp Gln Tyr Cys His Tyr Tyr Pro Glu Asn Ile
                                    340
Lys Pro Lys Pro Lys Leu Gln Glu Cys Asn Leu Asp Pro Cys Pro
                                    355
Ala Ser Asp Gly Tyr Lys Gln Ile Met Pro Tyr Asp Leu Tyr His
                                    370
Pro Leu Pro Arg Trp Glu Ala Thr Pro Trp Thr Ala Cys Ser Ser
                                    385
Ser Cys Gly Gly Ile Gln Ser Arg Ala Val Ser Cys Val Glu
                                    400
Glu Asp Ile Gln Gly His Val Thr Ser Val Glu Glu Trp Lys Cys
                                    415
                                                        420
```

```
Met Tyr Thr Pro Lys Met Pro Ile Ala Gln Pro Cys Asn Ile Phe
                425
Asp Cys Pro Lys Trp Leu Ala Gln Glu Trp Ser Pro Cys Thr Val
                440
Thr Cys Gly Gln Gly Leu Arg Tyr Arg Val Val Leu Cys Ile Asp
                                     460
His Arg Gly Met His Thr Gly Gly Cys Ser Pro Lys Thr Lys Pro
His Ile Lys Glu Glu Cys Ile Val Pro Thr Pro Cys Tyr Lys Pro
Lys Glu Lys Leu Pro Val Glu Ala Lys Leu Pro Trp Phe Lys Gln
                500
Ala Gin Glu Leu Glu Glu Gly Ala Ala Val Ser Glu Glu Pro Ser
                515
Phe Ile Pro Glu Ala Trp Ser Ala Cys Thr Val Thr Cys Gly Val
                530
Gly Thr Gln Val Arg Ile Val Arg Cys Gln Val Leu Leu Ser Phe
                545
                                    550
Ser Gln Ser Val Ala Asp Leu Pro Ile Asp Glu Cys Glu Gly Pro
                                    565
Lys Pro Ala Ser Gln Arg Ala Cys Tyr Ala Gly Pro Cys Ser Gly
                575
                                    580
Glu Ile Pro Glu Phe Asn Pro Asp Glu Thr Asp Gly Leu Phe Gly
                590
                                    595
                                                        600
Gly Leu Gln Asp Phe Asp Glu Leu Tyr Asp Trp Glu Tyr Glu Gly
                605
                                    610
Phe Thr Lys Cys Ser Glu Ser Cys Gly Gly Gly Val Gln Glu Ala
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                                    625
Val Val Ser Cys Leu Asn Lys Gln Thr Arg Glu Pro Cys
                635
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Ser Ser Arg Thr Gln Lys Leu Pro Thr Arg Asp Glu Glu Leu Phe
Gln Met Gln Ile Arg Asp Lys Ala Phe Phe His Asp Ser Ser Val
Ile Pro Asp Gly Ala Glu Ile Ser Ser Tyr Leu Phe Arg Asp Thr
                                     55
Pro Lys Arg Tyr Phe Phe Val Val Glu Glu Asp Asn Thr Pro Leu
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Ser Val Thr Val Thr Pro Cys Asp Ala Pro Leu Glu Trp Lys Leu
Ser Leu Gln Glu Leu Pro Glu Asp Arg Ser Gly Glu Gly Ser Gly
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<210> 125

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95
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 Asp Leu Glu Pro Leu Glu Gln Gln Lys Gln Gln Ile Ile Asn Glu
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 Glu Gly Thr Glu Leu Phe Ser Tyr Lys Gly Asn Asp Val Glu Tyr
                 125
                                     130
 Phe Ile Ser Ser Ser Pro Ser Gly Leu Tyr Gln Leu Asp Leu
                 140
 Leu Ser Thr Glu Lys Asp Thr His Phe Lys Val Tyr Ala Thr Thr
                 155
                                     160
 Thr Pro Glu Ser Asp Gln Pro Tyr Pro Glu Leu Pro Tyr Asp Pro
                 170
                                     175
 Arg Val Asp Val Thr Ser Leu Gly Arg Thr Thr Val Thr Leu Ala
                 185
                                     190
 Trp Lys Pro Ser Pro Thr Ala Ser Leu Leu Lys Gln Pro Ile Gln
                 200
                                     205
 Tyr Cys Val Val Ile Asn Lys Glu His Asn Phe Lys Ser Leu Cys
                 215
                                     220
Ala Val Glu Ala Lys Leu Ser Ala Asp Asp Ala Phe Met Ala
                 230
                                     235
 Pro Lys Pro Gly Leu Asp Phe Ser Pro Phe Asp Phe Ala His Phe
                 245
                                     250
Gly Phe Pro Ser Asp Asn Ser Gly Lys Glu Arg Ser Phe Gln Ala
                 260
                                     265
Lys Pro Ser Pro Lys Leu Gly Arg His Val Tyr Ser Arg Pro Lys
                 275
                                     280
Val Asp Ile Gln Lys Ile Cys Ile Gly Asn Lys Asn Ile Phe Thr
                 290
                                     295
Val Ser Asp Leu Lys Pro Asp Thr Gln Tyr Tyr Phe Asp Val Phe
                 305
                                     310
Val Val Asn Ile Asn Ser Asn Met Ser Thr Ala Tyr Val Gly Thr
                 320
                                     325
Phe Ala Arg Thr Lys Glu Glu Ala Lys Gln Lys Thr Val Glu Leu
                 335
                                     340
Lys Asp Gly Lys Ile Thr Asp Val Phe Val Lys Arg Lys Gly Ala
                350
                                     355
Lys Phe Leu Arg Phe Ala Pro Val Ser Ser His Gln Lys Val Thr
                365
                                    370
Phe Phe Ile His Ser Cys Leu Asp Ala Val Gln Ile Gln Val Arg
                380
                                    385
Arg Asp Gly Lys Leu Leu Ser Gln Asn Val Glu Gly Ile Gln
                395
                                    400
Gln Phe Gln Leu Arg Gly Lys Pro Lys Ala Lys Tyr Leu Val Arg
                410
                                    415
Leu Lys Gly Asn Lys Lys Gly Ala Ser Met Leu Lys Ile Leu Ala
                425
                                    430
Thr Thr Arg Pro Thr Lys Gln Ser Phe Pro Ser Leu Pro Glu Asp
                440
                                    445
Thr Arg Ile Lys Ala Phe Asp Lys Leu Arg Thr Cys Ser Ser Ala
                455
                                    460
Thr Val Ala Trp Leu Gly Thr Gln Glu Arg Asn Lys Phe Cys Ile
                470
                                    475
Tyr Lys Lys Glu Val Asp Asp Asn Tyr Asn Glu Asp Gln Lys Lys
                485
                                    490
Arg Glu Gln Asn Gln Cys Leu Gly Pro Asp Ile Arg Lys Lys Ser
                500
                                    505
Glu Lys Val Leu Cys Lys Tyr Phe His Ser Gln Asn Leu Gln Lys
                                    520
```

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Ala Val Thr Thr Glu Thr Ile Lys Gly Leu Gln Pro Gly Lys Ser 530 Tyr Leu Leu Asp Val Tyr Val Ile Gly His Gly Gly His Ser Val 545 Lys Tyr Gln Ser Lys Val Val Lys Thr Arg Lys Phe Cys

<210> 126 <211> 125 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 2493851 <400> 126 Met Trp Leu Val Gly Pro Ser Phe Leu Ser Cys Pro Leu Gly Lys 10 Val Pro Pro Ala Gly Leu Leu Ala Gly Ser Ser Gly Arg Gly 30 Ala Arg Arg Pro Ala Thr Pro Arg His Trp Ser Ser Thr Thr Pro 35 40 Gly Leu Arg Leu Glu Ala Pro Leu Cys Gln Leu Cys Pro Leu Gly 50 Gly Thr Arg Gln Asp Cys Gln Pro Leu Ser Trp Gln Val Thr Ser 60 65 70 Ala Phe Lys Leu Thr Val Pro Ser Pro Phe His Ala Pro Pro Arg 80 85 90 Ser Trp Ser Cys Leu Leu Gly Ile Phe Pro Gly Gln Ala Leu 95 100 Ala Leu Glu Pro Trp His Leu Phe Leu Gly Ser Met Leu Pro Arg 110 115 Cys Asp Gly Glu Cys

<210> 127 <211> 196 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 2495719 <400> 127

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35
                                     40
Thr Thr Ile Ile Glu Gly Arg Ile Thr Ala Thr Pro Lys Glu Ser
                 50
                                     55
Pro Asn Pro Pro Asn Pro Ser Gly Gln Cys Pro Ile Cys Arg Trp
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                                    70
Asn Leu Lys His Lys Tyr Asn Tyr Asp Asp Val Leu Leu Ser
                 80
                                    85
Gln Phe Ile Arg Pro His Gly Gly Met Leu Pro Arg Lys Ile Thr
                 95
                                    100
Gly Leu Cys Gln Glu Glu His Arg Lys Ile Glu Glu Cys Val Lys
                110
                                   115
Met Ala His Arg Ala Gly Leu Leu Pro Asn His Arg Pro Arg Leu
                125
                                   130
Pro Glu Gly Val Val Pro Lys Ser Lys Pro Gln Leu Asn Arg Tyr
                                    145
Leu Thr Arg Trp Ala Pro Gly Ser Val Lys Pro Ile Tyr Lys Lys
                155
                                    160
Gly Pro Arg Trp Asn Arg Val Arg Met Pro Val Gly Ser Pro Leu
               170
                                    175
Leu Arg Asp Asn Val Cys Tyr Ser Arg Thr Pro Trp Lys Leu Tyr
                                    190
His
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<211> 214 <212> PRT <213> Homo sapiens <220> <221> misc feature <223> Incyte Clone No: 2614153 <400> 128 Met Val Leu Gly Gly Cys Pro Val Ser Tyr Leu Leu Leu Cys Gly 10 Gln Ala Ala Leu Leu Cly Asn Leu Leu Leu His Cys Val Ser Arg Ser His Ser Gln Asn Ala Thr Ala Glu Pro Glu Leu Thr Ser Ala Gly Ala Ala Gln Pro Glu Gly Pro Gly Gly Ala Ala Ser Trp Glu Tyr Gly Asp Pro His Ser Pro Val Ile Leu Cys Ser Tyr 65 Leu Pro Asp Glu Phe Ile Glu Cys Glu Asp Pro Val Asp His Val 80 Gly Asn Ala Thr Ala Ser Gln Glu Leu Gly Tyr Gly Cys Leu Lys 100 Phe Gly Gly Gln Ala Tyr Ser Asp Val Glu His Thr Ser Val Gln 115 Cys His Ala Leu Asp Gly Ile Glu Cys Ala Ser Pro Arg Thr Phe 130 Leu Arg Glu Asn Lys Pro Cys Ile Lys Tyr Thr Gly His Tyr Phe 145 Ile Thr Thr Leu Leu Tyr Ser Phe Phe Leu Gly Cys Phe Gly Val

<210> 128

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      Asp
      Arg
      Phe
      Cys
      Leu Gly His Thr Gly Thr Ala Val Gly Lys Leu 170
      165

      Leu Thr Leu Gly Gly Leu Gly Ile Trp Trp Phe Val Asp Leu 11e
      185
      190
      195

      Leu Leu Leu Ile Thr Gly Gly Leu Met Pro Ser Asp Gly Ser Asn Trp 200
      200
      205
      210
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<210> 129 <211> 88 <212> PRT <213> Homo sapiens <220> <221> misc feature <223> Incyte Clone No: 2655184 Met Ala Cys Phe Ser Phe Phe Leu Cys Phe Leu Val His Leu Leu Ile Lys Met Asn Pro Val Thr Glu Ser Pro Ser Cys Leu Phe Ser 20 30 Pro Pro Ser Glu Ser Ala Leu Ala Ser Gln Leu Ala Leu Ser Ala 35 40 45 Ser Cys Asp Gln Arg Ala Pro Phe Ser Leu Ala Gly Val Val Ser 50 55 60 His Asp Pro Gly Trp Pro Val Val Arg Leu His Arg Pro Leu Val 65 70 Pro Glu His Ala Val Phe Ser Gln Pro Ser Leu Gln Pro

<210> 130 <211> 260 <212> PRT <213> Homo sapiens <220> <221> misc_feature <223> Incyte Clone No: 2848362

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                                     85
Gln Arg Val Val Ser Thr His Asn Leu Trp Leu Leu Ser Phe Leu
                 95
                                    100
Arg Arg Trp Asn Gly Ser Thr Ala Ile Thr Asp Asp Thr Leu Gly
                110
Gly Thr Leu Thr Ile Thr Leu Arg Asn Leu Gln Pro His Asp Ala
                125
                                    130
Gly Leu Tyr Gln Cys Gln Ser Leu His Gly Ser Glu Ala Asp Thr
                140
                                    145
Leu Arg Lys Val Leu Val Glu Val Leu Ala Asp Pro Leu Asp His
                                    160
Arg Asp Ala Gly Asp Leu Trp Phe Pro Gly Glu Ser Glu Ser Phe
                170
                                    175
Glu Asp Ala His Val Glu His Ser Ile Ser Arg Ser Leu Leu Glu
                185
                                    190
Gly Glu Ile Pro Phe Pro Pro Thr Ser Ile Leu Leu Leu Leu Ala
                200
                                    205
Cys Ile Phe Leu Ile Lys Ile Leu Ala Ala Ser Ala Leu Trp Ala
                215
                                    220
Ala Ala Trp His Gly Gln Lys Pro Gly Thr His Pro Pro Ser Glu
                230
                                    235
Leu Asp Cys Gly His Asp Pro Gly Tyr Gln Leu Gln Thr Leu Pro
                245
Gly Leu Arg Asp Thr
                260
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<223> Incyte Clone No: 2849906
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Gly Cys Cys Ala Leu Leu Leu Ser Leu Trp Ala Leu Cys Thr Ala
Cys Arg Arg Pro Glu Asp Ala Val Ala Pro Arg Lys Arg Ala Arg
                                     40
Arg Gln Arg Ala Arg Leu Gln Gly Ser Ala Thr Ala Ala Glu Ala
                                     55
Ser Leu Leu Arg Arg Thr His Leu Cys Ser Leu Ser Lys Ser Asp
                                     70
Thr Arg Leu His Glu Leu His Arg Gly Pro Arg Ser Ser Arg Ala
                                     85
Leu Arg Pro Ala Ser Met Asp Leu Leu Arg Pro His Trp Leu Glu
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Val Ser Arg Asp Ile Thr Gly Pro Gln Ala Ala Pro Ser Ala Phe
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<210> 131 <211> 295

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Pro His Gln Glu Leu Pro Arg Ala Leu Pro Ala Ala Ala Thr
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Ala Gly Cys Ala Gly Leu Glu Ala Thr Tyr Ser Asn Val Gly Leu
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                                    145
Ala Ala Leu Pro Gly Val Ser Leu Ala Ala Ser Pro Val Val Ala
                155
                                    160
Glu Tyr Ala Arg Val Gln Lys Arg Lys Gly Thr His Arg Ser Pro
                170
                                    175
Gln Glu Pro Gln Gln Gly Lys Thr Glu Val Thr Pro Ala Ala Gln
                                    190
Val Asp Val Leu Tyr Ser Arg Val Cys Lys Pro Lys Arg Arg Asp
                                    205
Pro Gly Pro Thr Thr Asp Pro Leu Asp Pro Lys Gly Gln Gly Ala
                                    220
Ile Leu Ala Leu Ala Gly Asp Leu Ala Tyr Gln Thr Leu Pro Leu
                230
Arg Ala Leu Asp Val Asp Ser Gly Pro Leu Glu Asn Val Tyr Glu
Ser Ile Arg Glu Leu Gly Asp Pro Ala Gly Arg Ser Ser Thr Cys
Gly Ala Gly Thr Pro Pro Ala Ser Ser Cys Pro Ser Leu Gly Arg
                275
Gly Trp Arg Pro Leu Pro Ala Ser Leu Pro
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<212> PRT
<213> Homo sapiens
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<221> misc_feature
<223> Incyte Clone No: 2899137
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Leu Gln Ala Ala Arg Gly Thr Trp Trp Asn Arg Pro Gly Gly Thr
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Ser Gly Ser Gly Glu Gly Val Ala Leu Gly Thr Thr Arg Lys Phe
Gln Ala Thr Gly Ser Arg Pro Ala Gly Glu Glu Asp Ala Gly Gly
Pro Glu Arg Pro Gly Asp Val Val Asn Val Val Phe Val Asp Arg
                 65
Ser Gly Gln Arg Ile Pro Val Ser Gly Arg Val Gly Asp Asn Val
Leu His Leu Ala Gln Arg His Gly Val Asp Leu Glu Gly Ala Cys
                 95
                                    100
Glu Ala Ser Leu Ala Cys Ser Thr Cys His Val Tyr Val Ser Glu
                110
                                    115
Asp His Leu Asp Leu Leu Pro Pro Pro Glu Glu Arg Glu Asp Asp
                125
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Met Leu Asp Met Ala Pro Leu Leu Gln Glu Asn Ser Arg Leu Gly
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<210> 132 <211> 183

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Cys Gln Ile Val Leu Thr Pro Glu Leu Glu Gly Ala Glu Phe Thr
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Leu Pro Lys Ile Thr Arg Asn Phe Tyr Val Asp Gly His Val Pro
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Lys Pro His
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<211> 113
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Ser Leu Phe Phe Leu Leu Ala Leu Asn Leu Pro Asp Val Phe Gly
                 20
                                     25
Leu Val Val Leu Pro Leu Glu Leu Lys Leu Arg Ile Phe Arg Leu
                 35
                                     40
Leu Asp Val Arg Ser Val Leu Ser Leu Ser Ala Val Cys Arg Asp
                 50
                                     55
                                                          60
Leu Phe Thr Ala Ser Asn Asp Pro Leu Leu Trp Arg Phe Leu Tyr
                 65
                                     70
                                                          75
Leu Arg Asp Phe Arg Gly Asp Phe Arg Asn Asp Ile Phe Thr Arg
                 80
                                     85
Lys Gly Ser Tyr Cys Leu Asp Tyr Ser Ala His Gln Lys Phe Leu
                                    100
Val Val Gly Phe Phe Cys Cys Lys
                110
```

35

40

Thr Ile Arg Asp Pro Glu Lys Pro Asn Thr Leu Glu Glu Leu Glu

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50
                                      55
                                                           60
Val Val Ser Glu Ser Cys Val Glu Val Gln Glu Ile Asn Glu Glu
                  65
                                      70
Glu Tyr Leu Val Ile Ile Arg Phe Thr Pro Thr Val Pro His Cys
                                      85
                                                          90
Ser Leu Ala Thr Leu Ile Gly Leu Cys Leu Arg Val Lys Leu Gln
                  95
                                     100
Arg Cys Leu Pro Phe Lys His Lys Leu Glu Ile Tyr Ile Ser Glu
                                     115
Gly Thr His Ser Thr Glu Glu Asp Ile Asn Lys Gln Ile Asn Asp
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Lys Glu Arg Val Ala Ala Met Glu Asn Pro Asn Leu Arg Glu
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Ile Val Glu Gln Cys Val Leu Glu Pro Asp
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agacaaagge tgttgateca etgaacecae eeagacaeta tgtggtttet tgaatgteet 180
acgtacattt tgatggatta cccaaggact atctgatgaa gaataataga gacatataaa 240
tacatatggg ctacatcttg gcaaaataaa gtaatcctga agtaaattct aaggatgttc 300
tgaattgaca cctcttaagc acaaccgaat gtcctggtgg ctttgcctcc cactggggct 360
ttttggctct tgtttggccc cagcggctgc tgcagctctg tctgaattca cacaggagca 420
acatgatggt gctcagccct cgccgaagtg tcttgctgaa gagttgggag atgcttggac 480
tattcagata gaagccaact ggaagtacag ggcagtcaac acaaaccaga gaggcaaact 540
tttggccagt gagacatgga aagggagaag aaatacattc ttctttctcc cctagagtga 600
ggaccaacct gagtcccagt cacctggaat cccctcagac gagcgtccct tgagatccag 660
cacatggcag ccagcgtgct gacgattcct tcctgcctac tggctccttc ttatttctgc 720
ctccgtggaa ctgtattctc taatcaatat tagcacatac atattgcccc agactgtacc 780
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caaaagaaaa atacaaaaaa aaaaa
                                                                   865
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<222> 11, 12
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<220>

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 ttgetggete ageetgetet ttgeteette atgggacece agtggateet geagttetge 180
 tettggetgg aaccaegeca gettegetgg agetggaetg ageegeettt tacattattg 240
gacteteteg ggttgagage tgcccaggae tcctgcagtt tcaccaccet tgttcctttg 300
actettgact cateatteat gacegttaac gtggttecat ttgtatggac ttettettte 360
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atagatgggg ttaccaggat tcaggctaca tggcctgagg caaggtcaca acatgagtga 480
cagaatgtgt cctggaagcc aggcatcctc tggggtgtat ttggggcgct caacaaggct 540
tgatcgagct ttgggggtag atctagctat tccatgggga ttcttttcag aattgctgtt 600
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attteteatg tatttttete atttatttat taatttttaa etgatagttg tacatatttg 420
ggggtacatg tgatatttgg atacatgtat acaatatata atgatcaaat cagggtaact 480
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cacccagget ggagtgcagt ggtgccatet cagettactg caacetetge etgecaggtt 600
caagcgattc tcatgcctcc acctcccaag tagctgggac tacaggcatg caccacaatg 660
cccaactaat ttttgtattt ttagtagaga cggggttttg ccatgttgcc caggctggcc 720
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                                                                  801
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 gcagagccat gatgagtctt acggaaataa ggttaaaaca tatgcttgaa atttggcatg 180
 gcagacaagc cagagcttgt gaaaatctaa gaaaccaaac acgtgtagcc accaaagtgg 240
 aaccacaaaa gggaagatct acagaaattt gttgccttgc tgtagttcca ttaaatgagg 300
 ttgtgcagtc aagcatcttg tggtgggtct ggagctgttg ccagcatcag gaagacaagc 360
 tgggtgctaa gtgaagaaat acacaatgta gaaactgtca ggcatctctg cccctggact 420
 teaccatate tgatgatgtt eteagagtea gggeaetget teaetttteg etteeaaate 480
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ggaaatggag tacccagata cccanngtga tatactttta tgccctcagt ttcttatctt 600
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getgaategg ggttaacate eetteeagge acagegagtt ggttetgett tttgeetgta 180
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gaactcagtg tcacagactc ttctgagtgt tttagggtca cagctagtgt aagaggcatg 300
aagaatagac atgcaaaagg gaacgggtgc accagagacc cctgttttgg ctgacagacc 360
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cettecagee tetggaagae actggeetge atcagttaga gteagageaa gtgteaette 660
acagggaaaa gaaggattat atagacttcc tatccctaga gtttataaat gtcaactata 720
taaaaaaagc tcaaaacagt gttaaaggaa tgaacagtag aattttaata ggctgtccaa 780
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aagggttact gagccacctt aagctagtac ctatatagta ggcaaaaagt acagaaatag 900
atgcaataag tgtggtgagt ctttgagcct acgagtcatg ccaccagcca taagttgacc 960
tatcacttga gaacctcctc agcaaagatg ccagaaaaca ttcaatcaag ttggcaaatg 1020
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cagcactgtc ctggagctaa tacactgttt cactgcctct gccatataat gatgccagca 1140
ctagccagct ggtgggtatt tggaggaatc ctgcatgagg attgcccaat aaggggcagg 1200
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ceteteaggt geceetactt getttetget teettetggt gaagtecace teeaacatta 180
acctgcccac cccacccccg tcatccctgg agaattccag ctttgtcgta tctcagagag 240
ggaatctaat tgtttttggg gggcaaaaga aagcaacgtt taggtatcac ttctacttgg 300
accgcatgcc tttttatagc caaatttctg tgtatttcgt aaatggattt cgcgttaatg 360
gatatttatg taataactag acttctcaga ttattgtgag aagggtcagg ttggaagggg 420
tgtaggaaga cgggtgaggg gtagttttt tctgtcctag ttttttttt ttttattgtc 480
atctctgagg tggactttgt cacctgtggt tattggggcc aagtggactc agctccgggg 540
gagaaggett etetgeeatt teggteeaan ggtgaetgae acaggegtae tttttgggae 600
tgtggaagca tcagatgcca gcactgactt cagaccagca nttcgggcta gaggaagatg 660
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tgcagccgcc agcatttctg cagcctggtg gctccacagg atctggtcca agctaccttt 180
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teteetteta ttaeceetgg gagttageea tagtteecaa egtgagaata teetggagae 300
ggggccactt ccacgggcag tccttctaca gcacaaggcc gccttccatt cacaaggatt 360
atgtgaaccg getetttetg aactggacag agggteagga gageggette etcaggatet 420
caaacctgcg gaaggaggac cagtctgtgt atttctgccg agtcgagctg gacacccgga 480
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